Differential Toxicity in Patients with and without DNA Repair Mutations: Phase I Study of Carboplatin and Talazoparib in Advanced Solid Tumors

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Abstract

Purpose: The PARP inhibitor (PARPi) talazoparib may potentiate activity of chemotherapy and toxicity in cells vulnerable to DNA damage.

Experimental Design: This phase I study evaluated the safety, tolerability, pharmacokinetics, and efficacy of talazoparib and carboplatin. Pharmacokinetic modeling explored associations between DNA vulnerability and hematologic toxicity.

Results: Twenty-four patients (eight males; 16 females) with solid tumors were enrolled in four cohorts at 0.75 and 1 mg daily talazoparib and weekly carboplatin (AUC 1 and 1.5, every 2 weeks or every 3 weeks), including 14 patients (58%) with prior platinum treatment. Dose-limiting toxicities included grade 3/4 neutropenia (63%), thrombocytopenia (29%), and anemia (13%). Grade 3 fatigue and grade 4 thrombocytopenia; the MTD was not reached. Grade 3/4 toxicities included fatigue (13%), neutropenia (63%), thrombocytopenia (29%), and anemia (38%). After cycle 2’s dose, delays/reductions were required in all patients. One complete and two partial responses occurred in germline BRCA1/2 (gBRCA1/2) patients. Four patients showed stable disease beyond 4 months, three of which had known mutations in DNA repair pathways. Pharmacokinetic toxicity modeling suggests that after three cycles of carboplatin AUC 1.5 every 3 weeks and talazoparib 1 mg daily, neutrophil counts decreased 78% [confidence interval (CI), 87–68] from baseline in gBRCA carriers and 63% (CI, 72–55) in noncarriers (P < 0.001). Pharmacokinetic toxicity modeling suggests an intermittent, pulse dosing schedule of PARP inhibition, differentiated by gBRCA mutation status, may improve the benefit/risk ratio of combination therapy.

Conclusions: Carboplatin and talazoparib showed efficacy in DNA damage mutation carriers, but hematologic toxicity was more pronounced in gBRCA carriers. Carboplatin is best combined with intermittent talazoparib dosing differentiated by germline and somatic DNA damage mutation carriers. Clin Cancer Res 23(21): 6400–10. ©2017 AACR.

Introduction

PARPs comprise a family of enzymes that play an integral role in DNA repair through the process of base excision (1). Decreased activity of PARP results in the accumulation of single-strand breaks in DNA, which eventually leads to DNA double-strand breaks (1). The cell’s inability to repair this damage by homologous recombination (HR) double-strand DNA repair can prove lethal (2). BRCA1 and BRCA2 are important members of the HR pathway. Hence, BRCA-deficient tumors are more susceptible to the effects of PARP inhibition (PARPi). PARPi therapy is now approved for patients with germline BRCA-mutated (gBRCA) ovarian cancer in the third-line setting as well as in ovarian cancers harboring somatic mutations in BRCA1/2 (3, 4). More recently, it has been approved as maintenance therapy for recurrent platinum-sensitive ovarian cancer (5). Talazoparib is a potent PARPi (6) that shows antitumor cytotoxicity at much lower concentrations than other PARPi, such as olaparib, rucaparib, and veliparib (7). Talazoparib is in late stage clinical development as a single agent and has shown significant antitumor activity in gBRCA patients with ovarian cancer and breast cancer (8, 9). PARPi, such as talazoparib, may potentiate the activity of chemotherapy agents that interfere with DNA repair. Synergy may occur through their inhibition of the catalytic activity PARP1 or by trapping PARP1 to DNA at sites of DNA single-strand breaks, leading to delays in repair and in subsequent accumulation of single-strand DNA breaks (10, 11). Carboplatin is an alkylating chemotherapeutic producing interstrand DNA cross-links and is approved in several cancer subtypes (12). PARP inhibitors may perturb nucleotide excision repair (NER; refs. 13, 14) after carboplatin exposure, and synergy may occur by decreasing the ability to remove inter- and intranucleosomal DNA damage.
Pharmacokinetic/toxicity modeling and in vitro assays suggest an intermittent pulse dosing schedule may have a more favorable benefit/risk ratio than continuous daily dosing of PARPi in combination with platinum chemotherapy.

Studies show that tumors with a broader subset of mutations in DNA repair, beyond BRCA1/2, respond to PARPi therapy (16). Patients with mutations in proteins involved in DNA damage repair by HR also showed increased sensitivity to PARP inhibition (2, 17, 18). Similarly, early studies show that platinum therapies are especially effective in tumors with DNA repair mutations irrespective of tissue origin (19). Although PARPi combined with chemotherapy showed objective responses in some patients (20–25), the combination of PARPi with cytotoxic chemotherapy has been hampered by overlapping toxicities, thereby limiting the dose of the PARPi and/or chemotherapy (21, 25). Therefore, low initial doses of both drugs may be needed to avoid dose-limiting toxicity. Carboplatin given at an AUC of 1.5 to 2 mg/L/min per week has been shown to have lower hematologic toxicity without jeopardizing clinical benefit when compared with carboplatin AUC of 6 mg/L/min every 3 weeks (26–28). Thus, in this trial, we used carboplatin AUC 1.5 mg/L/min per week as a starting dose combined with talazoparib 0.75 mg daily (75% of the MTD).

This phase I trial was designed to determine the safety, feasibility, and recommended phase II doses of carboplatin and talazoparib in advanced, metastatic solid tumors in patients with and without germline DNA repair defects. Despite planning relatively low starting doses, post cycle 2 hematologic toxicities required dose delays/reductions in all patients. Given the frequency of dose alterations holds and the complexity of comparing pharmacokinetics and dosing among patients, we used a pharmacokinetic–toxicity model to determine the toxicity profile and included in vitro efficacy data to support optimal dosing regimens in gBRCA carriers and noncarriers.

**Patients and Methods**

**Study population**

Patients with advanced solid tumors who had received any number of prior lines of systemic therapy including carboplatin or PARPi were enrolled. Patients were required to have an ECOG performance status of ≤2, absolute neutrophil count >1.5 x 10^9/L, hemoglobin (Hgb) ≥9.5 g/dL, Platelets (plt) ≥100 x 10^9/L, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit normal (ULN), total bilirubin <1.5 x ULN, creatinine <1.5 x ULN or creatinine clearance >60 mL/minute. Key exclusion criteria included known allergic reaction or poor tolerability to PARPi, carboplatin, and untreated brain metastases. Patients were enrolled after giving verbal and written consent, and study approval was obtained from the federal agency, Institutional Review Boards at the University of California, San Francisco (San Francisco, CA) and regulatory authorities (NCT02358200). The study followed the Declaration of Helsinki and appropriate clinical practice guidelines.

**Treatment and study assessments**

The study was designed as a phase 1, open-label, 3 + 3 dose escalation/expansion trial of daily oral talazoparib in combination with carboplatin administered 2 or 3 weeks out of a 3-week cycle after a 1-day treatment run-in period (Supplementary Table S1). The starting dose and schedule of carboplatin and talazoparib was 1.5 mg/mL x min weekly (75% single-agent MTD) and 0.75 mg (75% of single-agent MTD) daily, respectively. Treatment was continued until disease progression by RECIST 1.1, unacceptable toxicity, or withdrawal from study. Dose-limiting toxicities (DLTs) were defined as any grade 3 or higher nonhematologic treatment-related adverse event or grade 4 neutropenia lasting >7 days, febrile neutropenia, grade 3 thrombocytopenia with bleeding, or grade 4 thrombocytopenia. Failure to receive at least 75% of doses in cycle 1 (first 21 days) due to toxicity was considered a DLT, and patients who missed more than 25% of doses for reasons other than toxicity had to be replaced.

**Pharmacokinetic assessments.** Carboplatin blood concentrations were determined using a validated high-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) method during cycle 1 day 1 (prior to talazoparib dosing) and cycle 2 day 1 predose and up to 24 hour postdose in cohort 1. Carboplatin exposures were described using a three-compartment model (Supplementary Data S3). Talazoparib concentrations were measured at cycle 1 day 8, cycle 1 day 15, and cycle 2 day 1 using HPLC MS/MS in 15 patients. Talazoparib exposures were characterized using a two-compartment model. The lower limit of quantification was 2.00 mg/L for carboplatin and 25 pg/ml for talazoparib.

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Statistical methods for toxicity and efficacy analyses. Spearman rank correlation, Pearson correlation, and linear regression were used to explore relationships among continuous variables, and Mann–Whitney tests were used to explore relationships of variables within subgroups of patients, respectively. Kaplan–Meier survival curves were used to assess the association between DNA damage–related proteins and progression-free survival. In the latter analysis, patients with germline variants of unknown significance (VIS) were considered as nonmutated. Data analyses and visualization were managed using R [R-3.1.1, Development Core Team (2013)].

Pharmacokinetic–toxicity model analyses. Nonlinear mixed-effects modeling were used for all pharmacokinetics and pharmacokinetic–toxicity analysis (NONMEM VII Software, ICON Development Solutions). Individual and population pharmacokinetic parameters for clearance, maximum concentration (Cmax), area under the concentration–time curve (AUC) after the first cycle dosing (AUCcycle) were estimated as further described in Supplementary Data S1–S3.

A previous developed semimechanistic hematologic toxicity model (30) was used to estimate the toxic effect of the combination of talazoparib and carboplatin on the number of circulating platelets and white blood cells (further described in Supplementary Data S1–S3).

Deterministic and stochastic simulations from the final pharmacokinetics–toxicity model parameters were used to estimate the optimal dose and schedule of the treatment combination (Supplementary Data S12). Three scenarios were tested: (i) lowering the daily dose of talazoparib; (ii) lowering the dose and frequency of the chemotherapy agent; and (iii) using pulse dosing of PARPi in combination with chemotherapy; a short period of dosing of the PARPi combined with a normal mono-therapy dose of carboplatin followed by a recovery period. Using these simulations, a dose in which <30% of patients showed grade 3 or 4 neutropenia within the first three cycles was considered tolerable. The model assumptions for therapeutic clinical concentrations for talazoparib were derived from reported in vitro concentrations that achieved at least 50% reduction in cell growth (IC50) in triple-negative breast cancer cell lines (TNBC), either as a single agent or in combination with carboplatin as described by Hassan and colleagues (31). As talazoparib is highly bound in human plasma, the obtained IC50 values were adjusted for protein binding in human plasma for comparison of equivalent unbound concentrations (32). In each of the dosing schedule, the time above the effective concentration in gBRCA patients and noncarriers was predicted.

Results

Baseline characteristics and patient disposition

A total of 24 patients were enrolled between February 2015 and January 2016. Baseline characteristics, such as blood counts, disease, and age, did not differ between gBRCA carriers and noncarriers (Table 1). The majority of patients (58%) had received platinum prior to enrollment; one patient progressed on prior olaparib immediately prior to study entry and had previously progressed on platinum. Patient disposition is shown in Table 1. The median duration of treatment was 11 weeks (range, 1–77 weeks). Reasons for treatment discontinuation included progression of disease (79%), unacceptable toxicity (13%), or another unrelated adverse event (4%). One patient remains on study with a continued partial response (PR).

Safety results

Across the entire study cohort, treatment-related adverse events of any grade severity experienced on study consisted of neutropenia, anemia, thrombocytopenia, fatigue, headache, insomnia, nausea, and vomiting. Two dose-limiting toxicities were observed, including grade 4 thrombocytopenia and grade 3 fatigue (Table 2). Post cycle 2 hematologic toxicities required dose delays/reductions in all patients. Because of the inability to deliver the planned schedule, the trial was stopped early prior to reaching an MTD. Grade 3/4 toxicities included neutropenia (63%), anemia (50%), thrombocytopenia (33%), and fatigue (13%; Table 2). Dose reductions and/or treatment interruptions were required post cycle 2 in all patients (Table 2). No differences were seen in baseline counts between gBRCA patients and non-BRCA carriers (Table 2; Fig. 1), but there was a trend toward greater absolute decrease from baseline in neutrophil (P = 0.090) and total WBC.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Study cohort (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>59 (42–77)</td>
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<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<tr>
<td>Caucasian</td>
<td>19</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
</tr>
<tr>
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</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
</tr>
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<td>ECOG performance status</td>
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<tr>
<td>0</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>1</td>
<td>24 (75%)</td>
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<tr>
<td>Tumor histology</td>
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<tr>
<td>Breast</td>
<td>11 (46%)</td>
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<tr>
<td>Prostate</td>
<td>5 (21%)</td>
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<tr>
<td>Ovarian</td>
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<tr>
<td>Cancer of unknown primary</td>
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<tr>
<td>Cholangiocarcinoma</td>
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<tr>
<td>Other*</td>
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<tr>
<td>Number of lines of prior therapy</td>
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<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>3 (22%)</td>
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<tr>
<td>2</td>
<td>3 (22%)</td>
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<td>3</td>
<td>3 (22%)</td>
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<td>≥6</td>
<td>5 (21%)</td>
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<td>Prior platinum therapy</td>
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</tr>
<tr>
<td>Progressed on platinum</td>
<td>8 (33%)</td>
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<tr>
<td>Prior PARP inhibitor</td>
<td>1 (4%)</td>
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<tr>
<td>Genetic mutations</td>
<td></td>
</tr>
<tr>
<td>Germline BRCA1/2</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>Somatic mutations in DNA repair</td>
<td>3 (12%)</td>
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<tr>
<td>VUS in DNA repair (somatic/germline)</td>
<td>6 (25%)</td>
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<tr>
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<td>4 (16%)</td>
</tr>
<tr>
<td>Negative</td>
<td>4 (16%)</td>
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<tr>
<td>Patient disposition</td>
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<tr>
<td>Reasons for study discontinuation, n (%)</td>
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<tr>
<td>Disease progression</td>
<td>19 (79%)</td>
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<tr>
<td>Unacceptable toxicity</td>
<td>3 (12.5%)</td>
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<tr>
<td>Unrelated adverse event</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Therapy ongoing</td>
<td>1 (4%)</td>
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</table>

*Other cancers: Adenoid cystic carcinoma and urothelial carcinoma.
Table 2. Cohorts, doses, toxicities, and dose interruptions and reductions

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Dosing schema</th>
<th>Toxicity all grades</th>
<th>Dose delivery</th>
<th>Transfusions/growth support</th>
<th>Filgrastim use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3S</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Talazoparib (PO) mg/day</td>
<td>Carboplatin AUC (i.v.)</td>
<td>DLT</td>
<td>Dose interruptions</td>
<td>RBC transfusion</td>
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<tr>
<td></td>
<td></td>
<td>0.75</td>
<td>15 (2/3 weeks)</td>
<td>1: G3 Fatigue</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1.5 (2/3 weeks)</td>
<td>1: G4 Thrombocytopenia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1.5 (3/3 weeks)</td>
<td>2: 14.2%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1.5 (3/3 weeks)</td>
<td>1: 14.2%</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: DLT, dose-limiting toxicity; IV, intravenous; N, number of patients; PO, orally; RBC, red blood cell.

(P = 0.091) at the start of cycle 2 in gBRCA patients compared with non-BRCA carriers (Supplementary Table S1; Fig. 1B).

Efficacy analyses

Twenty-one patients were evaluable for objective response. Three patients (14%) showed a partial or complete response. Durable responses of >12 months were seen in two patients (21 and 18+ months) and one remains on therapy (Fig. 2A and C). One patient with PR had BRCA2-mutated bladder cancer and the other two patients had TNBC (TNBC, BRCA1, CR; BRCA2, PR).

Eleven of 21 evaluable patients (52%) experienced disease stabilization (range, 7–22 weeks; median, 10.5 weeks). Of the four patients with stable disease beyond 4 months, three had mutations in DNA repair genes with the fourth patient having no known genetic sequencing, including a somatic BRCA2 mutation, a BRCA2 VUS/ATR VUS and a BRI1 germline mutation. Seven patients (33%) showed progressive disease (three gBRCA 1/2 mutation carriers, one noncarrier, one patient with a somatic FANCC mutation, and three unknown carriers, Fig. 2D). As stated previously, 14 patients (58%) on this trial were previously exposed to platinum. Among those previously exposed to platinum, five of 14 patients (35%) had stable disease on this trial and another one patient had a PR. The patient with BRCA2-mutated bladder cancer had three prior lines of platinum therapy with initially platinum-sensitive disease. He had a PR on this trial. In addition, a prostate cancer patient with a somatic BRCA2 mutation had 12 prior cycles of carboplatin prior to trial initiation and had confirmed stable disease on this trial for 5 months.

The median duration on treatment was 11 weeks (range, 1–77 weeks). Figure 2A shows that dose holds of carboplatin and talazoparib preceded disease progression in almost all patients. The maximum percent change from baseline in tumor measurements is shown in Fig. 2B. Of 21 evaluable patients, 16 had measurable disease, two patients had disease progression before the treatment scan, and three had nonmeasurable disease. One patient had prior progression on both carboplatin and olaparib prior to the study and had stable disease on this trial. In this small dataset, there was a trend toward prolonged progression-free survival for patients with either germline or somatic mutations in DNA damage repair genes compared with noncarriers (HR, 2.568, P = 0.0728; Fig. 2C).

Pharmacokinetics

Talazoparib plasma concentrations are shown in Fig. 3A. Talazoparib pharmacokinetic model results are shown in Fig. 3B, and the parameter estimates are shown in Fig. 3C. In this dataset, no correlations were observed between pharmacokinetic estimates and age, sex, BSA, GFR (using MDRD formula), and weight. Exposures appeared to increase in a dose proportional manner in this study (0.75 or 1 mg), and the estimated talazoparib clearance in gBRCA carriers was not statistically different from noncarriers of talazoparib (Supplementary Fig. S2).

Pharmacokinetic–toxicity model analyses

The predicted neutrophil and platelet count by pharmacokinetic–toxicity model and observed counts is shown in Fig. 4A for representative patients with and without germline BRCA mutations, respectively. After accounting for variability in baseline, drug exposures and dosing regimen, the pharmacokinetic/toxicity model predicts that for a dosing schedule of carboplatin AUC 1.5 mg/mL × min weekly and talazoparib 1 mg continuous daily dosing (Fig. 4B, schedule A), the percent decrease in neutrophil and platelet counts from baseline is predicted to be significant larger in gBRCA carriers (−78%; 95% confidence interval (CI), −87 to −68) than noncarriers (−68%; −85 to −61; P < 0.001; Fig. 4C; Supplementary Table S2). Similarly, the relative decrease in platelet count from baseline is predicted to be significantly larger in gBRCA carriers (−68%; 95% CI, −85 to −61) than noncarriers (−59%; −69 to −54, P < 0.001; Fig. 4C; Supplementary Table S2).

The pharmacokinetic/toxicity model was used to estimate the optimal dosing schedule of the combination Optimized talazoparib. Simulations suggest that maintaining talazoparib at 1 mg per day (100% of the MTD) would require...
substantial dose reductions of carboplatin to avoid >30% grade 3/4 hematologic toxicity: AUC of 1.5 every 4 weeks (schedule C) in gBRCA carriers, and AUC 3 monthly in noncarriers (schedule D; Fig. 4D and E; Supplementary Table S3). In these schedules, the carboplatin dose would need to be reduced below the standard monthly dose (33, 34).

**Optimized carboplatin.** Alternatively, simulations show that if carboplatin is given at an AUC 1.5 weekly, a dose decrease to 10% to 20% of the MTD of single-agent talazoparib would provide acceptable rates of hematologic toxicity [0.1 mg daily in gBRCA carriers and 0.2 mg in noncarriers (schedule E/F); Fig. 4D and E]. In these schedules, talazoparib dosing does not lead to concentrations above the the in vitro derived protein binding–adjusted concentration at 50% response (IC50) for gBRCA/somatic DNA repair gene mutations (3 ng/mL) nor for noncarriers (12 ng/mL; ref. 31; Supplementary Table S3).

**Optimized combination.** Simulations factoring in vitro efficacy data suggested that the combination may be optimized best by introducing talazoparib-free periods (pulse dosing). To keep both agents close to their suggested single-agent dose, the number of doses of talazoparib should be reduced to 50% to 60% of continuous dosing to provide acceptable rates of hematologic toxicity (Fig. 4D and E; Supplementary Table S3), while retaining a significant amount of time above in vitro IC50 of talazoparib (3 ng/mL in gBRCA or somatic DNA repair gene mutations and 12 ng/mL in noncarriers; Fig. 4F, Supplementary Table S3; ref. 31). Pharmacokinetic–toxicity modeling supports using talazoparib at 0.75 mg daily (on days 1–14 per month) with carboplatin AUC 6 monthly in gBRCA carriers (schedule G) and carboplatin AUC 1.5 weekly and talazoparib at 1 mg daily on days 1–4 weekly in non-gBRCA carriers (schedule H; Fig. 4D–F).

**Discussion**

There has been significant clinical interest in exploiting the vulnerability of DNA repair linked to germline and somatic mutations in tumors. The successful introduction of PARPi has led to further studies to combine PARPi with chemotherapy to explore the potential for chemopotentiation and synthetic lethality with other agents that cause DNA damage (10, 11). Combination chemotherapy and PARPi may cause overlapping toxicity in vulnerable cells, such as the hematopoietic cells, and therefore limit dosing of such combination, particularly in patients with germline BRCA mutations (11, 23, 24). We performed a clinical trial to determine whether the combination of carboplatin and talazoparib would be both effective and tolerable in a heavily pretreated group of patients with and without BRCA mutations. The results suggest that at 0.75 and 1 mg daily talazoparib and weekly carboplatin (AUC 1 and 1.5, every 2 weeks or every 3 weeks), the combination carries an unacceptable risk every 2 or 3 weeks of hematologic toxicity, especially in patients with germline BRCA mutations, and in vitro studies suggest that the achieved serum concentrations of talazoparib are not predicted to be efficacious in noncarriers. Therefore, the originally planned dose expansion in TNBC and patients with germline mutations were abandoned. The combination of PARPi and carboplatin could potentially be further explored in patients with mutations in DNA repair, but only after considerable attention to modification of dosing schedule, including potential pulse dosing of PARPi.

Several studies have evaluated the efficacy of platinum and PARPi in different populations to understand the ideal population for either or both of these agents. Updates to the CALGB/Alliance 40603 study presented at the San Antonio Breast Cancer Symposium in 2015 did not show an improved disease-free survival with the addition of carboplatin to neoadjuvant chemotherapy in TNBC patients (event-free survival HR, 0.84; 95% CI, 0.58–1.22; ref. 35). However, a more detailed analysis of the results of the CALGB 40603 suggested that a subset of patients with a homologous repair deficiency (defined as either higher homologous recombination deficiency score or primary tumor BRCA positivity) was found to be more likely to benefit from DNA-damaging agents rather than all women with TNBC (34). Similarly, PARPi has shown to be much more efficacious in patients with mutations in DNA repair genes (16, 36, 37).
three patients with a CR or PR in this study had gBRCA mutations, and of four patients with stable disease beyond 4 months, two had somatic BRCA mutations and one a BRIP1 germline mutation, suggesting increased benefit in tumors vulnerable to DNA damage. The results of the current study and prior studies lead us to believe that future combination trials of PARPi and carboplatin should be further explored in patients with mutations in DNA repair mechanisms.
Despite the potential for increased efficacy in patients with DNA repair mutations, results from the seven patients with gBRCA suggest that patients with germline mutations in DNA repair genes had more toxicity with this synthetic lethal combination compared with the 17 non/unknown carriers. Significant decreases in blood counts were observed by cycle 2 in all patients in the study, leading to post cycle 2 hematologic toxicities requiring dose delays/reductions in all patients. Despite the significant neutropenia seen in our trial, the prophylactic use of growth factor was limited in this trial due to daily dosing of talazoparib and historic concerns for simultaneous use of hematopoietic growth factors and chemotherapy (38). Thus, pulse dosing of PARPi may also allow for increased use of growth factor support. The degree of neutropenia and cytopenias was more pronounced in gBRCA carriers, suggesting an increased susceptibility of hematopoietic cells that harbor the germline defect in DNA repair. This is supported by the findings of...
Figure 4.
Plots of the blood counts time and efficacy profiles between gBRCA and non-BRCA mutation carriers. 4A, Plot of two selected individuals to show the neutrophil count (blue) profiles and platelet count (red) profiles in a patient with gBRCA and a noncarrier. For each patient, dose delivery is shown using the concentration–time profiles of carboplatin and talazoparib. The predicted time above IC\text{50} for talazoparib is shown in green. 4B, Planned and optimized dosing schedules for BRCA mutation carriers ascertained from pharmacokinetic toxicity modeling using three scenarios: (i) lowering the dose and frequency of carboplatin (schedule C/D); (ii) lowering the daily dose of talazoparib (schedule E/F); and (iii) using pulse dosing of PARPi in combination with chemotherapy: a short period of dosing of the PARPi combined with normal dose of carboplatin followed by a recovery period (schedule G/H). 4C, Visualization of the estimated differences in neutrophil (top) and platelet (bottom) toxicity in gBRCA and noncarriers in the planned dosing schedule (schedule A). 4D, Predicted toxicity over time of each of the optimized dosing schedules. 4E, Predicted grade of neutropenia (with ranges) within the first three cycles for the planned (schedule A) and optimized dosing schedules (schedule C–F) in BRCA1/2 and non-BRCA mutation carriers. 4F, The predicted time above the in vitro derived IC\text{50} for the PARPi of the planned dosing schedule (schedule A), the observed dosing schedule (schedule B), and the optimized, pulse dosing schedule in the gBRCA1/2 (schedule G) and non–BRCA mutation carriers (schedule H), as an estimate of expected efficacy. Specifically here in gray, the expected time above the in vitro–derived, protein-binding adjusted, IC\text{50} of 3 ng/mL (31) in somatic DNA repair gene mutation is shown as compared with the estimated time above the protein-adjusted IC\text{50} of 12 ng/mL (31) in noncarriers using the optimized dosing schedule (schedule H). Figure 4A. Arrow = blood transfusions (violet); dark red bar = dose holding of talazoparib. IC\text{50} = concentration leading to 50% reduction in cell growth; Here the protein binding-adjusted talazoparib IC\text{50} concentration was estimated as 3 ng/mL in gBRCA or somatic DNA repair gene mutations and 12 ng/mL in noncarriers (31).
Baert and colleagues, who showed an increased chromosomal radiosensitivity in healthy carriers of heterozygous BRCA1 mutations (39). Retrospective analyses by Huazno and colleagues suggest that anthracycline-based chemotherapy caused more pronounced neutropenia in gBRCA carriers compared with noncarriers after chemotherapy or radiotherapy (40). However, other studies have not noticed any differential toxicity, leading to the hypothesis that a synthetic lethal combination is required to produce this result. For instance, Drooger and colleagues found no differences in toxicity after anthracyclines or taxane treatment between gBRCA carriers compared with noncarriers (41). Specifically, they saw no differences in dose holds/dose delays or rates of febrile neutropenia between carriers and noncarriers (41). Early-phase clinical trials of the PARPi olaparib, reported no differences in tolerability or toxicity between BRCA mutation subgroups (42). The recent phase III trial (NOVA3) evaluating niraparib as maintenance therapy in platinum-sensitive recurrent ovarian cancer–stratified patients according to presence or absence of a germline BRCA mutation (gBRCA cohort or non-gBRCA cohort; ref. 5). Although this study and others (including Part 1 of ARIEL2) have stratified efficacy results by mutational subgroup, the safety and toxicity data were not analyzed per subgroup (NOVA3, rucaparib; refs. 5, 43). As mentioned above, it may be that a synthetic lethal combination of PARPi and chemotherapy is needed to produce this differential toxicity between germline BRCA mutation carriers and noncarriers. Potentially, PARPi monotherapy in gBRCA patients can undergo effective DNA repair in bone marrow tissue that has not experienced loss of heterozygosity, but a synthetic lethal combination overcomes these normal DNA repair processes.

Because of the inability to deliver the planned schedule, the trial was stopped early prior to reaching an MTD. Thus, optimal intermittent dosing regimens were explored in this trial through pharmacokinetic modeling and further supported using in vitro experiments. The concept of pulse dosing as a strategy to minimize toxicity and maintain efficacy has been explored in prior trials and preclinical research. Lopez and colleagues recently suggested that a more biological meaningful strategy for developing drug combinations may be to use 100% of the optimal biological dose of both drugs in the combination, but introduce alternate dosing schedules to improve tolerability (44). Previous phase II trial results of olaparib and veliparib suggest that chemotherapy combined with pulse PARPi dosing [noncontinuous dosing to allow a treatment-free period each cycle, e.g., using PARPi dosing at day 1 or day 1–4 only (21), day 1–7 (22), or day 1–14 (20) per 3 week cycle] resulted in a more favorable toxicity profile (20–22) compared with continuous dosing of the PARPi (11, 23, 24). Antitumor activity observed in these pulse dosing schedules and effective concentrations derived from in vitro studies justifies further evaluation of the pulse dosing in the combination to understand if efficacy can be retained with pulse dosing (20–22).

Wilson and colleagues recently published the results of a relevant phase I study examining the combination of rucaparib with carboplatin in patients with advanced solid tumors (45). Here, the MTD was found to be rucaparib 240 mg once daily, days 1 to 14 in combination with carboplatin AUC 5 every 28 days. This dose and interval of rucaparib is much lower than the recommended phase II dose in ovarian cancer of 600 mg twice daily. Of note, this dosing regimen is not dissimilar to what we have proposed in this article, whereby when PARPi and carboplatin are combined, the carboplatin dose remains high (comparable with the single-agent MTD) with a reduction in the dose interval of the PARPi. Encouragingly, of patients who received oral rucaparib and carboplatin, 63.6% achieved disease control for greater than or equal to 12 weeks, and PRs were reported in three patients with ovarian or breast cancer, two of whom had a known BRCA mutation.

The BROCADE phase II study showed a trend but did not meet its significance cutoff when evaluating progression-free survival benefit in patients with locally advanced or metastatic BRCA-mutant breast cancer treated with carboplatin/paclitaxel and veliparib 120 mg day 1 to 7 per 3 weekly cycle (30% of the MTD) versus carboplatin/paclitaxel and placebo (46). It remains unclear whether results from the BROCADE study can be extrapolated to our trial given the differences in population and PARPi.

The results of our clinical trial add to the existing literature that modeling is imperative when designing clinical trials when trying to minimize toxicity and optimize efficacy.

Concluding Remarks

In summary, the combination of carboplatin and talazoparib showed responses in (germline and somatic) DNA damage mutation carriers, but significant overlapping hematologic toxicity prevented effective drug delivery of the combination of carboplatin and talazoparib. Hematologic toxicity was more pronounced in gBRCA carriers. Pharmacokinetic–toxicity models factoring in in vitro derived IC_{50} suggest that combination therapy may be optimized best by introducing talazoparib-free periods (pulse dosing), with dosing schedules differentiated for germline and purely somatic DNA damage mutations carriers.
Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Correction: Differential Toxicity in Patients with and without DNA Repair Mutations: Phase I Study of Carboplatin and Talazoparib in Advanced Solid Tumors

In this article (Clin Cancer Res 2017;23:6400–10), which was published in the November 1, 2017, issue of Clinical Cancer Research (1), the two lines in Fig. 3B denoting IC50 for noncarriers versus those with BRCA1/2 mutations were reversed. The corrected version of Fig. 3 is provided below. The publisher regrets this error.

Reference


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