Clinical Studies

Phase I Study of PARP Inhibitor ABT-888 in Combination with Topotecan in Adults with Refractory Solid Tumors and Lymphomas

Shivaani Kummar1,2, Alice Chen2, Jiuping Ji3, Yiping Zhang3, Joel M. Reid4, Matthew Ames4, Lee Jia2, Marcie Wei2, Giovanna Speranza2, Anthony J. Murgo2, Robert Kinders3, Lihua Wang3, Ralph E. Parchment3, John Carter3, Howard Stotler3, Larry Rubinstein2, Melinda Hollingshead2, Giovanni Melillo3, Yves Pommier1, William Bonner1, Joseph E. Tomaszewski2, and James H. Doroshow1,2

Abstract

A phase I trial of ABT-888 (veliparib), a PARP inhibitor, in combination with topotecan, a topoisomerase I–targeted agent, was carried out to determine maximum tolerated dose (MTD), safety, pharmacokinetics, and pharmacodynamics of the combination in patients with refractory solid tumors and lymphomas. Varying schedules and doses of intravenous topotecan in combination with ABT-888 (10 mg) administered orally twice a day (BID) were evaluated. Plasma and urine pharmacokinetics were assessed and levels of poly(ADP-ribose) (PAR) and the DNA damage marker γH2AX were measured in tumor and peripheral blood mononuclear cells (PBMC). Twenty-four patients were enrolled. Significant myelosuppression limited the ability to coadminister ABT-888 with standard doses of topotecan, necessitating dose reductions. Preclinical studies using athymic mice carrying human tumor xenografts also informed schedule changes. The MTD was established as topotecan 0.6 mg/m2/d and ABT-888 10 mg BID on days one to five of 21-day cycles. Topotecan did not alter the pharmacokinetics of ABT-888. A more than 75% reduction in PAR levels was observed in 3 paired tumor biopsy samples; a greater than 50% reduction was observed in PBMCs from 19 of 23 patients with measurable levels. Increases in γH2AX response in circulating tumor cells (CTC) and PBMCs were observed in patients receiving ABT-888 with topotecan. We show a mechanistic interaction of a PARP inhibitor, ABT-888, with a topoisomerase I inhibitor, topotecan, in PBMCs, tumor, and CTCs. Results of this trial reveal that PARP inhibition can modulate the capacity to repair topoisomerase I–mediated DNA damage in the clinic. Cancer Res; 71(17): 5626–34. ©2011 AACR.

Introduction

PARP enzymes are involved in the recognition of DNA damage and the facilitation of DNA repair. Inhibition of PARP activity is a promising approach for enhancing the DNA-damaging effects of chemotherapeutic agents (1, 2). PARP inhibitors in clinical development have generated considerable interest for patients whose tumors are driven by BRCA1 or BRCA2 mutations, based on reports of increased sensitivity of homozygous BRCA-deficient cells to PARP inhibition (3, 4).

ABT-888 (veliparib) is a potent, orally administered small molecule inhibitor of PARP-1 and PARP-2. In preclinical models, ABT-888 potentiates the antitumor activity of multiple cytotoxic agents, including topoisomerase I–targeted inhibitors (5). PARP inhibition prevents efficient repair of DNA damage induced by camptothecins (6–10). Therefore, we hypothesized that coadministration of ABT-888 with topotecan would enhance the antitumor activity of this topoisomerase I inhibitor.

We conducted a phase I trial of ABT-888 combined with topotecan hydrochloride in patients with advanced, refractory solid tumors and lymphomas. The objectives were to establish the safety, tolerability, and maximum tolerated dose (MTD) of the combination of ABT-888 with topotecan; to evaluate the pharmacokinetics of each agent alone and in combination; and to determine the effects of the study treatment on the level of PARP activity and DNA damage in peripheral blood mononuclear cells (PBMC), circulating tumor cells (CTC), and tumor biopsy samples.

Patients and Methods

Eligibility

Patients eligible for this trial had histologically documented solid tumors and low-grade lymphoid malignancies that were refractory to standard therapy; an Eastern Cooperative

Authors' Affiliations: 1Center for Cancer Research and 2Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda; 3Applied/Developmental Research Support Directorate, Science Applications International Corporation-Frederick, Inc., National Cancer Institute, Frederick, Maryland; and 4Mayo Clinic, Rochester, Minnesota

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Corresponding Author: James H. Doroshow, Center for Cancer Research and Division of Cancer Treatment and Diagnosis, National Cancer Institute, Building 31, Room 3N44, 31 Center Drive, NIH, Bethesda, MD 20892. Phone: 301-496-4291; Fax: 301-496-0826; E-mail: doroshoj@mail.nih.gov

Oncology Group performance status ≤2; and adequate organ and marrow function defined as leukocytes ≥3,000/µL, absolute neutrophil count ≥1,500/µL, platelets ≥100,000/µL, total bilirubin ≤1.5 × the upper limit of normal (ULN), aspartate aminotransferase and/or alanine aminotransferase ≤2.5 × ULN, and creatinine <1.5 × ULN.

Prior anticancer therapy must have been completed at least 4 weeks prior to enrollment. Prior therapy with a PARP inhibitor was allowed. Patients were excluded if they had an uncontrolled intercurrent illness or were pregnant or lactating.

This trial was conducted under a National Cancer Institute (NCI)-sponsored IND with Institutional Review Board approval. The protocol design and conduct complied with all applicable regulations, guidance, and local policies. ClinicalTrials.gov identifier: NCT00553189.

Trial design

This was an open-label, single-arm phase I study of the combination of ABT-888 administered orally with topotecan hydrochloride administered intravenously in patients with advanced malignancies. ABT-888 was supplied under a Collaborative Research and Development Agreement between the Division of Cancer Treatment and Diagnosis, NCI, and Abbott Laboratories, Inc. Topotecan was obtained from commercial sources.

To evaluate the pharmacokinetics and pharmacodynamics of each agent alone compared with the combination, we initially evaluated a schedule of topotecan administered alone on day 8, followed a week later by ABT-888 administered twice a day (BID) on days 1 to 7, and topotecan on days 2 to 5 for cycle 1. Starting on cycle 2, ABT-888 was administered on days 1 to 7 and topotecan on days 1 to 5 (21-day cycle; Fig. 1, schedule A). The starting dose was topotecan 1.2 mg/m²/d and ABT-888 10 mg BID (dose level 1; Table 1). However, we observed grade 4 myelosuppression at this dose level, initially necessitating dose reduction of topotecan to 0.9 mg/m²/d with ABT-888 10 mg BID, followed by a revision of the drug administration schedule. We hypothesized that administering a dose of topotecan a week before giving 4 additional days of topotecan with 5 days of ABT-888 may be priming bone marrow progenitors, increasing the likelihood of myelosuppression (11). Therefore, we revised the schedule to administer topotecan on days 1 to 5 and ABT-888 on days 2 to 5 in cycle 1 and then gave both drugs together on days 1 to 5 in subsequent cycles (21-day cycles; Fig. 1, schedule B). The topotecan dose was reduced to 0.75 mg/m²/d. However, we again observed grade 3 and 4 myelosuppression, resulting in reduction of the topotecan dose to 0.6 mg/m²/d given on days 1 to 5 (dose level −3). This dose level was well tolerated. Because of the clinical toxicities, human xenograft model studies were carried out indicating that delivering 1 day of ABT-888 with 5 days of topotecan produced the same antitumor effect as 5 days of both drugs (Fig. 2). Therefore, to safely escalate the dose of topotecan, we explored administering topotecan at 0.75 mg/m²/d given on days 1 to 5, with ABT-888 administration on day 1 only in each cycle (21-day cycles; Fig. 1, schedule C).

Adverse events were graded according to NCI Common Terminology Criteria version 3.0. Dose-limiting toxicity (DLT) was defined as an adverse event that occurred in the first 2 cycles (given that the schedules were different between cycles 1 and 2), was believed to be study drug related, and fulfilled one of the following criteria: grade 3 or higher nonhematologic toxicity (except for nausea/vomiting and diarrhea without maximal symptomatic/prophylactic treatment); grade 4...
thrombocytopenia; grade 4 neutropenia lasting 5 days or more; or febrile neutropenia. Any degree of anemia, leukopenia in the absence of neutropenia as defined above, or lymphopenia was not considered dose limiting. Patients were not allowed to receive prophylactic growth factors for the first 2 cycles.

Three patients were initially enrolled per dose level. Patient enrollment and dose escalation followed a traditional 3+3 design. The MTD was defined as the dose at which no more than 1 of 6 patients or 33% or less experienced a DLT (one dose level below the dose at which at least 2 of 3 to 6 patients experienced DLT).

Safety and efficacy evaluations
A complete patient history and physical examination were conducted at baseline and prior to each cycle. Complete blood counts with differential and serum chemistries were done at baseline, weekly for the first 2 cycles, and then prior to each cycle. More frequent blood counts were done for patients experiencing grade 3 and 4 myelosuppression to determine the duration of neutropenia and thrombocytopenia and to document recovery. Radiographic evaluation was done at baseline and every 2 cycles to assess for tumor response based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.0; ref. 12).

Pharmacokinetics
Blood samples (7 mL) for pharmacokinetic analysis were collected during cycle 1 at baseline prior to drug administration and 0.5, 1, 2, 4, 7, 10, and 24 hours postdose on days −8, 1, and 2 for dose levels 1 and −1; days 1 and 2 for dose levels −2 and −3; and days 1 and 3 for dose level 1A.

A urine sample of 10 mL was collected before drug administration and at every void from 0 to 24 hours postdose on the same days that blood was collected for pharmacokinetic analysis.

Total topotecan plasma concentrations were measured by high-performance liquid chromatography (HPLC) with fluorescence detection as previously described (13). ABT-888

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<th>Table 1. Dose levels, number of patients enrolled, and dose-limiting toxicities in cycles 1 and 2</th>
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aOne patient progressed before completing 2 cycles so was not evaluable for toxicity and was therefore replaced. Abbreviation: C, cycle.

Figure 2. Tumor growth delay with revised ABT-888 and topotecan dosing schedules in mice bearing A375 human melanoma xenografts. Topotecan (1.5 mg/kg) was administered by intraperitoneal injection once a day for 5 consecutive days (QD × 5) starting on study day 9. ABT-888 (3.13 mg/kg) was administered orally starting on study day 9 as follows, relative to topotecan: 1 hour before the first dose (QD × 1), first and second doses (QD × 2), first, second, and third doses (QD × 3), and first, second, third, fourth, and fifth doses (QD × 5). The antitumor efficacies of the revised dose schedules (1, 2, or 3 days of ABT-888 administration in combination with 5 days of topotecan), measured on day 31, were not significantly different from 5 days of ABT-888 administration. Animal weight loss did not exceed 10% in any cohort. Data presented as mean ± SD.
plasma concentrations were measured by an HPLC-based method (14) modified to include drug isolation by solid-phase extraction by using a Bond Elut Certify (Varian) column and fluorescence (excitation, 255 nm and emission, 390 nm) detection (R. Klecker, personal communication). Additional details are included in the Supplementary Appendix. Topotecan and ABT-888 plasma concentration–time data were analyzed by standard noncompartmental methods by using the program WinNonlin Pro (Pharsight Corp).

**Pharmacodynamics**

Blood samples for PBMCs were collected in 8-mL Cell Prep Tubes (Becton Dickinson) before drug treatment and 2, 4, 7, and 24 hours after drug administration on the first day of topotecan alone, ABT-888 alone, and the combination. PBMCs were isolated as previously described (15). A pretreatment biopsy was obtained just prior to drug administration on study, and a postdose biopsy was collected 3 to 7 hours after administration of the combination. Levels of poly(ADP-ribose) (PAR), a product of PARP, were measured by using a validated chemiluminescent PAR immunoassay as previously described (15, 16). Blood samples were also collected pre- and postdosing (day 2 or 5) to examine the effect of the combination on phosphorylated histone H2AX (γH2AX), a marker for the formation of DNA double-strand breaks, in CTCs by using a quantitative, validated assay (17).

γH2AX was also measured in tumor samples by using a quantitative immunofluorescence assay as previously described (18). γH2AX in PBMCs was measured as described in the Supplementary Appendix.

**Human tumor xenograft models**

Xenograft models were used before and during the trial to help determine an optimum clinical dosing schedule. The effects of ABT-888, topotecan, or the combination on tumor growth were assessed in athymic nude (nu/nu NCr) mice bearing A375 (topotecan sensitive) human melanoma xenografts as described in the Supplementary Appendix. A375 cells were obtained from American Type Culture Collection, cultured for less than 6 months, and not reauthenticated.

**Results**

**Patient demographics**

A total of 24 patients were enrolled between November 2007 and June 2009 (Table 2). All patients had previously received prior standard therapy and had evidence of disease progression. In the initial cohorts, most patients had received more than 5 prior systemic therapies (range 2–14). In light of the degree of myelosuppression observed, we enrolled less heavily pretreated patients (3 or fewer prior systemic therapies) starting with patient 13.

**Toxicity**

We observed 3 DLTs in the first 6 patients enrolled on dose level 1 (ABT-888 10 mg BID on days 1 to 7; topotecan 1.2 mg/m²/d on day −8 and days 2 to 5 in cycle 1 and on days 1 to 5 in cycle 2 onward; schedule A, Fig. 1). One patient developed grade 4 neutropenia and thrombocytopenia, one had grade 4 neutropenia lasting longer than 5 days, and one had febrile neutropenia. All 6 patients experienced grade 3 or 4 myelosuppression in the first 2 cycles, necessitating a topotecan dose reduction to dose level −1 (0.9 mg/m²/d). One patient developed grade 4 neutropenia for longer than 5 days, meeting the criteria for DLT. Because 2 other patients on this dose level also developed grade 4 neutropenia (even though it was less than 5 days in duration), the dose level was not considered tolerable. The drug administration schedule was revised to reduce the number of days of ABT-888 dosing, eliminate treatment on day −8, and further reduce the dose of topotecan (schedule B, Fig. 1). On dose level −2, topotecan (0.75 mg/m²/d) was administered on days 1 to 5 of every cycle, with ABT-888 (10 mg BID) administered on days 2 to 5 in cycle 1 and days 1 to 5 in cycle 2 onward. Three patients were enrolled and 2 DLTs were observed, febrile neutropenia and grade 4 neutropenia lasting more than 5 days. This necessitated a reduction in topotecan dose to 0.6 mg/m²/d for dose level −3; 3 patients were treated at this dose level, and no DLTs were observed.

In view of the toxicities observed, we then employed xenograft models to explore alternative dosing schedules in
an attempt to escalate both agents. Results from these studies indicated that 1 day of ABT-888 administration (dose of 3.13 mg/kg) with 5 days of topotecan (1.5 mg/kg) produced a nearly equivalent antitumor effect as 5 days of both drugs (Fig. 2, Supplementary Table S1). On the basis of these preclinical data, we amended the trial to evaluate escalating the dose of topotecan while reducing the duration of ABT-888 administration to 1 day only (schedule C, Fig. 1). Five patients were enrolled on dose level 1A, and 2 developed grade 4 thrombocytopenia, meeting criteria for DLT. Three additional patients were enrolled on dose level −3; no DLTs were observed. Thus, the MTD was established as topotecan 0.6 mg/m²/d on days 1 to 5 and ABT-888 10 mg BID on days 1 to 5 in 21-day cycles.

Efficacy

Four of 6 patients on dose level 1 had stable disease after 2 cycles; however, these patients were taken off study because of toxicity. One patient with Hurthle cell thyroid cancer received a total of 33 cycles on dose level −3 with disease stabilization. One patient (dose level −3) with refractory melanoma received a total of 14 cycles with disease stabilization. One patient with colorectal cancer and one with bile duct adenocarcinoma (both on dose level 1A) received total of 6 and 4 cycles, respectively, with disease stabilization.

Pharmacokinetics

The mean (± SD) half-life for topotecan administered alone, 1 week before beginning combination treatment (schedule A), was 3.6 ± 3.0 hours, with mean (± SD) clearance and steady-state volume of distribution values of 9.2 ± 5.0 L/hr/m² and 35.1 ± 17.3 L/m³, respectively. The mean (± SD) half-life, clearance, and steady-state volume of distribution values for topotecan after administration of ABT-888 were 3.0 ± 1.4 hours, 9.8 ± 5.1 L/hr/m², and 35.7 ± 16.3 L/m³, respectively. Topotecan half-life, clearance, and steady-state volume of distribution values were also not altered by concomitant administration with ABT-888 in schedules B and C (data not shown). Topotecan was predominantly excreted in the urine: 24 hours after intravenous administration, the cumulative urinary recovery of total topotecan (mean ± SD) ranged from 94.1% ± 29.5% (day 1, n = 11) to 105.1% ± 16.7% (day 2) of the administered doses. The mean values (± SD, n = 9) for maximum plasma concentration, time to maximum plasma concentration, half-life, and area under the concentration-time curve extrapolated to infinity for ABT-888 (10 mg, BID) administered alone in schedule A were 262 ± 80 nmol/L, 1.6 ± 1.1 hours, 4.4 ± 1.4 hours, and 1,460 ± 450 nmol/L•h, respectively. When administered with topotecan in schedules B and C, the values were 255 ± 125 nmol/L, 1.8 ± 0.9 hours, 4.9 ± 1.8 hours, and 1,740 ± 786 nmol/L•h, respectively. Thus, there was no evidence of a significant pharmacokinetic interaction between the 2 drugs.

Pharmacodynamics

A summary of pharmacodynamic responses for patients in this trial is included in Supplementary Table S2. PARP was modulated by ABT-888 for each of the administration schemes studied and in the majority of patients. Topotecan did not seem to alter the ability of ABT-888 to inhibit PARP. In PBMCs, a greater than 50% mean reduction in PAR was observed after administration of ABT-888 in all dose levels, except for the level with the highest dose of topotecan (1.2 mg/m²/d; Fig. 3A). Supplementary Figure S1 shows data by schedule for the 23 patients with evaluable PBMC PAR levels. A greater than 75% reduction in PAR levels in tumors was observed in each of the 3 patients for whom paired tumor biopsies were available (Fig. 3B); 2 of these patients also had a greater than 60% reduction in PAR levels in PBMCs. The baseline PAR level in PBMCs from the third patient was below the required minimum for analysis.

Levels of γH2AX were measured in PBMCs after administration of topotecan alone and after the combination. One of 3
patients had elevated levels of γH2AX in PBMCs after a dose of 0.75 mg/m²/d topotecan alone, but elevations were not observed with lower doses. However, after topotecan was given with ABT-888, PBMCs from 2 of 7 patients on dose level –3 (0.6 mg/m²/d topotecan) and all 3 patients on dose level –2 (0.75 mg/m²/d topotecan) showed increases in γH2AX (Fig. 4A). The increases in γH2AX were small but tended to be greater with the higher topotecan dose (dose level –2). By 24 hours after dosing, γH2AX levels had returned to baseline levels. The two patients on dose level –3 who had increased γH2AX levels in PBMCs after administration of ABT-888 with topotecan also had a reduction in PAR in PBMCs. These patients had a 100% PAR reduction in PBMCs at 2 hours postdose and 100% and 76.3% reductions at 4 hours postdose, compared with a 60.2% ± 29.6% PAR reduction (mean ± SD) at 2 hours postdose for the 5 patients on that dose level in whom a γH2AX response was not observed (4 hours; 73.5% ± 22.1%). Paired tumor biopsies from 2 patients, one on dose level –1 and one on dose level –3, were analyzed for γH2AX, but no effect of study treatment on γH2AX levels was measured (data not shown).

Total CTCs and the number of γH2AX-positive CTCs were measurable in samples from 4 patients at baseline and after combined ABT-888 and topotecan treatment (Fig. 5A and B). The percentage of γH2AX-positive CTCs increased in 3 of the 4 patients. The average increase for the 4 patients was 23% (95% CI: 5–40; the change is nonnegative with 0.06 significance, 1 sided, by the nonparametric sign test). Interestingly, whereas the patient with the highest total number of CTCs, patient 21, had a decrease in total CTCs after treatment, this patient had an increase in the percentage of γH2AX-positive CTCs. Data from day 5 were available from one patient (patient 24). For this patient, the fraction of CTCs positive for γH2AX increased from 16% at baseline to 100% by day 5, whereas the number of CTCs remained constant.

Discussion

This trial evaluated the toxicities, pharmacokinetics, and pharmacodynamics of ABT-888, a potent PARP inhibitor, in combination with a topoisomerase I inhibitor in clinical use, topotecan, in patients with advanced malignancies. The definition of DLT included drug-related adverse events that occurred in the first 2 cycles (given that the schedules were different between cycles 1 and 2). As 6 evaluable patients received at least 2 cycles without DLT at dose level –3, which included the regimen of a full 5 days of dosing of both ABT-888 and topotecan starting with cycle 2, this regimen
was established as the MTD (topotecan administered intravenously at 0.6 mg/m²/d on days 1 to 5 and ABT-888 given orally at 10 mg BID on days 1 to 5, in 21-day cycles). Myelosuppression was the principal toxicity on this trial, which is consistent with the severe neutropenia in 65% to 75% of courses and severe thrombocytopenia in 25% to 30% of courses when topotecan is administered to patients with lung or ovarian cancer at FDA-approved doses of 1.5 mg/m²/d for 5 days with 2 dose reductions allowed to 1 mg/m²/d (19, 20). Combination trials of topotecan with other cytotoxics such as cisplatin have required dose reduction of topotecan to 0.75 mg/m²/d or lower (21). Because of the degree of myelosuppression observed with topotecan alone, especially in heavily pretreated patients, it is difficult to draw conclusions about the contribution of ABT-888 to the toxicity of the combination regimen.

We used preclinical models during the conduct of the trial to evaluate our clinical observations and to revise the trial design. Although preclinical models indicated a better safety profile for 1 day of ABT-888 in combination with 5 days of topotecan, we were unable to dose escalate topotecan in the clinic by reducing the number of days of ABT-888. It seems likely that a major reason for our difficulty in translating the results of our modeling of the ABT-888 plus topotecan combination in A375 melanoma xenografts to the clinic is the remarkable tolerance of mouse (versus human) bone marrow progenitors to topotecan (22).

One important question in developing PARP modulators is whether coadministration of a PARP inhibitor with reduced doses of topotecan results in superior benefit-to-risk profiles than full doses of topotecan alone. Enhanced normal tissue toxicity has been an important consideration in combination trials of PARP inhibitors with cytotoxic chemotherapies, requiring chemotherapeutic dose reductions (23, 24). As exemplified by our trial and trials with other PARP inhibitors in combination with chemotherapy, it has been difficult to define an optimum combination dose and schedule that would improve the therapeutic ratio. This could not be addressed in the current phase I dose escalation study because of a relatively small number of patients with a variety of refractory tumors. On the basis of our recent study in cancer cell lines with XPF-ERCC1 inactivation, it is possible that the potential benefit of using PARP inhibitors and topoisomerase I–targeted drugs will be seen in tumor cells with preexisting DNA repair deficiencies (10). To determine the effect of underlying genetic defects in the DNA repair pathways, such as ATM, ATR, BRCA, XRCC, XPF, and Fanconi anemia pathway, we are conducting this analysis in tumor samples from patients in our ongoing trial of the combination of ABT-888 with cyclophosphamide.

This is the first clinical study showing significant reduction in PAR levels (more than 75%) in all 3 paired tumor biopsies compared with baseline after administration of ABT-888 at 10 mg. Similar reductions were also observed in PBMCs. Whether this degree of PARP inhibition is sufficient (or a higher degree of inhibition is needed) to derive clinical benefit is currently unknown, making it difficult to define the “optimal biologic dose” of ABT-888 in combination with chemotherapy. Escalating the PARP inhibitor dose to the MTD may not be necessary to derive clinical benefit, especially given the narrow therapeutic index of certain combination regimens.

As previously reported in our phase 0 study of ABT-888 (15), tumor cells are more sensitive to PARP inhibition than PBMCs. Therefore, we evaluated the number of CTCs and the presence of γH2AX in these tumor cells as a marker of drug effect on tumor. γH2AX is a sensitive marker of DNA damage (18, 25). We hypothesized that increased DNA damage caused by the addition of an inhibitor of DNA repair, ABT-888, to topotecan could produce a measurable increase in γH2AX levels in surrogate tissue and tumor (10). We observed an increase in γH2AX in PBMCs after treatment with the combination of ABT-888 and topotecan when compared with topotecan alone. We did not observe a change in γH2AX in the 2 paired tumor biopsies examined. The lack of increased γH2AX in tumor biopsy samples may reflect an actual absence of effect on the level of DNA damage in tumor, given the low dose of topotecan administered, or the fact that tumor biopsy

**Figure 5.** A, total CTCs isolated from patients on dose level 3 and 1A; data on day 5 was only available from patient 24. B, percentage of CTCs positive for γH2AX from the same patient samples.
timing was optimized to observe effects on PAR levels, and not γH2AX levels, which are transient.

CTCs offer a relatively noninvasive way to repeatedly sample tumor cells over time, allowing assessment of dynamic markers. An increase in γH2AX in CTCs following administration of topotecan has been previously reported by our group (17). In the current trial, we detected an increase in the fraction of CTCs positive for γH2AX in 3 of 4 patients for whom CTC data were available after administration of the combination of topotecan with ABT-888 (Fig. 5). In the only patient in whom posttreatment samples were obtained at day 5 (following completion of all doses of study drugs), γH2AX levels increased from 16% at baseline to 100%, suggesting an appreciable DNA damage response to drug treatment. This is the first clinical trial showing an increase in a marker of DNA damage in CTCs following administration of the combination of a PARP inhibitor with chemotherapy. The significance of these findings will be explored in further clinical trials. The actual number of CTCs collected (less than 10 at all time points in 3 of 4 patients) illustrates one of the major challenges for the wider application of CTCs to assess drug effect on target (Fig. 5B). Thus, newer technologies for CTC capture, which have been reported to substantially increase the number of CTCs harvested from a patient, could have a great impact on the future utility of CTCs as pharmacodynamic markers in clinical trials.

We investigated varying schedules of ABT-888 administration with topotecan in xenograft models after encountering toxicities with the initial schedule. Efficacy was equivalent whether ABT-888 was administered for 1 to 2 days or 5 days (with shorter treatment being better tolerated). This raises the question of the duration of exposure to PARP inhibitors necessary to derive clinical benefit. Ongoing clinical trials investigating combinations of PARP inhibitors with cytotoxic chemotherapies commonly evaluate multiple days of PARP inhibitor administration before, during, and after chemotherapy, in an attempt to increase DNA damage and delay DNA repair. The xenograft experiments carried out during this trial challenge the dogma that more is better. Issues such as chronic versus intermittent schedules and optimal sequencing based on kinetics of DNA damage caused by the cytotoxic agent need to be explored further in clinical trials to maximize clinical benefit while ensuring patient safety. Further characterization of tumor-specific genetic defects in DNA repair and checkpoint pathways might also reveal the patients whose tumors will respond best to a combination of PARP- and topoisomerase I-targeted therapies.

Enhancing the therapeutic ratio between tumor cell killing and bone marrow toxicity for the combination of ABT-888 and topotecan will require evaluation of multiple, pharmacodynamically driven treatment schedules in the clinic. However, to our knowledge, this is the first clinical trial showing a mechanistic interaction between a PARP inhibitor and a topoisomerase I inhibitor in PBMCs, tumor, and CTCs. Results of this trial show that a PARP inhibitor can modulate the capacity to repair topoisomerase I–mediated DNA damage in the clinic.

Disclosure of Potential Conflicts of Interest

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