Detection of Poly(ADP-ribose) Polymerase Cleavage in Response to Treatment with Topoisomerase I Inhibitors: A Potential Surrogate End Point to Assess Treatment Effectiveness

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INTRODUCTION

PARP is a nuclear protein activated by single- and double-stranded DNA breaks (1) and involved in multiple processes including DNA replication (2), DNA repair (3, 4), cell differentiation (5), transformation (6) and cell cycle regulation (7, 8). Cleavage of PARP and other proteins occurs during cell death (9–11). A variety of stimuli (12–15) induce a caspase-mediated proteolytic cleavage of PARP between Asp 216 and Gly 217, which divides the NH2-terminal DNA-binding domain of PARP from its COOH-terminal catalytic domain (12, 13), generating two fragments of about M, 90,000 and M, 26,000. We have shown previously in several different cell types that the Topo I inhibitor-induced cleavage of PARP is characteristic of PCD and is proportional to the number of apoptotic cells measured by acridine orange staining (15). Although PARP cleavage has been shown previously to occur as part of PCD in human cell lines in culture, this event has not been demonstrated to occur in human tissues undergoing PCD in vivo.

Camptothecin analogues, which function as Topo I inhibitors, are presently in clinical use for therapy of several tumor types and are under extensive investigation and therapeutic evaluation in a number of clinical trials (17–24). Preclinical and clinical studies show great promise for the use of the camptothecin analogues CPT-11 (18–24), TPT (18, 20, 25), and 9-ami nocamptothecin (17, 18, 20) as chemotherapeutic agents. CPT-11 has been shown to have clinical effectiveness against advanced colorectal cancers (21–24). Topo I inhibitors are known to bind to the complex formed between the nuclear enzyme Topo I and DNA throughout the cell cycle (26). The ternary complex confers higher stability to the Topo I-DNA ligand, thus hampering the relaxation of Topo I-linked single-strand breaks. These events initiate the activation of the apoptotic pathway that culminates with cleavage of PARP and DNA fragmentation (13–15). We have described previously the kinetics of the effect of Topo I inhibitors on PARP cleavage and PCD in various cell lines (15) and their effect on the growth rate of SW480 colon cancer xenografts (25). The goals of this study were: (a) to determine whether PARP cleavage could be used as a marker of PCD in colon cancer cell lines; (b) to assess whether PARP cleavage could be used as an early marker to predict response to Topo I inhibitors in vivo; and (c) to determine whether tumors in humans demonstrate PARP cleavage in response to chemotherapy with CPT-11. The studies were carried out with colon cancer cell lines growing in tissue culture, with xenografts growing in athymic mice, as well as with metastatic tumors in patients with colon cancer.

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3 The abbreviations used are: PARP, poly(ADP-ribose) polymerase; PCD, programmed cell death; Topo, topoisomerase; TPT, topotecan; CPT-11, irinotecan; FBS, fetal bovine serum; CT, computed tomography.
MATERIALS AND METHODS

Cell Lines. VACO5, VACO6, VACO8, VACO451, VACO425, and VACO411 colon cancer cell lines are from the Case Western Reserve University cell line bank (27). SW480 and HCT116 colon cancer cells were obtained from the American Type Culture Collection. VACO5, VACO6, VACO8, and HCT116 cells were maintained in MEM with Earle’s salts supplemented with 0.1 mM nonessential amino acids (Grand Island Biological Co., Grand Island, NY) and 8% heat-inactivated FBS. VACO411 and VACO425 were grown in the same medium but supplemented with 2% FBS. VACO 451, VACO 411, and VACO 425 were, in addition, maintained in the presence of insulin (10 μg/ml; Sigma Chemical Co., St. Louis, MO), 300 μM ascorbate, 2.5 mM pyruvate, and 2 mM L-glutamine (Grand Island Biological Co.). VRC5 human colon cancer cells (obtained from Dr. P. J. Houghton, St. Jude Children’s Research Hospital, Memphis, TN; Ref. 28) and SW480 human colon cancer cells were grown in DMEM containing 10% FBS. All cells were maintained in culture at 37°C in an atmosphere of 5% CO₂.

Treatment in Vitro. Cells in early logarithmic growth were cultured in T75 polystyrene flasks and treated with 0.01, 0.1, 1, or 10 μM TPT or 20 μM CPT-11 for 24, 48, or 72 h, as indicated for each particular experiment. TPT was from the Drug Synthesis and Chemistry Branch of the National Cancer Institute (Bethesda, MD), and CPT-11 was from Pharmacia & Upjohn, Inc. (Kalamazoo, MI). Control samples treated with 1:1000 DMSO from Fisher Scientific (Fair Lawn, NJ), used as vehicle, were included. At the end of each treatment, all cells within the culture (suspension and trypsinized cells) were pooled, an aliquot was taken for acridine orange staining, and within the culture (suspension and trypsinized cells) were vehicle, were included. At the end of each treatment, all cells were immediately frozen in liquid nitrogen and stored at −80°C for further analysis of PARP cleavage by Western blotting (15).

Acridine Orange Staining. To 10 μl of the cell suspension were added 10 μl of a 100 μg/ml solution of acridine orange in PBS. A minimum of 100 cells/count was counted using a fluorescence microscope. The cells with condensed chromatin were counted as acridine orange positive, whereas those with a homogeneous chromatin pattern were counted as acridine orange negative (15, 29, 30). Condensation of chromatin in apoptotic bodies is a hallmark of apoptosis but not necrosis.

Xenograft Generation and Animal Treatment. Four-week-old, female, athymic mice (athymic nude; Ireland Cancer Center Athymic Animal Facility), about 20–22 g body weight, were inoculated s.c. on both sides, behind the anterior forelimb with 5 × 10⁶ cells in 0.2 ml of serum-free MEM as described previously (25). Each group was comprised of eight animals each or 16 xenografts. Animals were maintained under pathogen-free conditions. After xenografts reached about 50 mm³ in size, animals were treated with Topo I inhibitors as follows. Vehicle solution (1:1000 DMSO in PBS) or Topo inhibitor were administered i.p. in the doses and times indicated for each experiment. Selection of doses was based on previous reports and was in the range of the maximum tolerated dose. Growth curves were performed in five of the eight animals by externally measuring tumors in three dimensions using a caliper. Tumor volume (V) was determined by the following equation: 

\[ V = L \times W \times H \times 0.5236, \]

where L is length, W is the width, and H is the height of the xenograft (31). The remaining three animals were sacrificed 24 h after the last drug dose, and the xenografts were resected. Xenografts were then instantly frozen in liquid nitrogen and stored at −80°C for further analysis of PARP cleavage by SDS-PAGE (Refs. 15 and 32) and Western blotting (15).

Biopsies of Tumor Metastasis from Patients in Phase II Clinical Trial with CPT-11. After signing informed consent, patients with metastatic colon cancers were administered a 90-min infusion of 125 mg/m² CPT-11. Samples from metastatic tumors in the liver, pelvis, or retroperitoneum were obtained with a 14-gauge needle biopsy under CT guidance immediately before treatment and 24 h after treatment. The tissues were immediately frozen in liquid nitrogen and stored at −80°C for analysis of PARP cleavage by Western blotting procedure. Tumor biopsy specimens were divided into sections to analyze the biochemical parameters and confirm tumor histology.

Origin of Antibodies. A monoclonal antibody to purified human PARP, named 4C10-5, was developed and isolated by protein A/G Sepharose chromatography in our laboratories. The antibody is an IgG1κ that shows specificity for the NAD binding domain of PARP and reacts with the Mr 116,000 enzyme as well as with the Mr 90,000 degradation product in human cells (15, 16, 33). This antibody is now commercially available (PharMingen, San Diego, CA). Monoclonal mouse Ab-1 to actin was from Oncogene Science (Uniondale, NY). Peroxidase-linked anti-mouse immunoglobulin from sheep was from Amersham (Arlington Heights, IL).

Western Blotting. Cells and xenograft samples were sonicated in a lysis buffer comprised of 0.5% sodium deoxycholate, 0.2% SDS, 1% Triton X-100, 1% NP40, 5 mM EDTA, 10 μg/ml leupeptin, 10 μg/ml aprotinin, and 1 mM phenylmethylsulfonyl fluoride in PBS (reagents were from Sigma Chemical Co., St. Louis, MO). Samples (35 μg of protein measured by the bicinchoninic acid method, 0.05% v/v) SDS (2% w/v), Tris (118 mM), glycerol (10%), and traces of bromphenol blue to the final concentrations indicated. Samples were then boiled in a 100°C water bath for 5 min and separated by SDS-PAGE consisting of a 5% (w/v) acrylamide stacking gel and a 12.5% (w/v) acrylamide separating gel containing 0.1% SDS (32). The running buffer was comprised of 0.1% SDS, 25 mM Tris, and 250 mM glycine (pH 8.3). Electrophoretic fractionation was carried out at a constant current of 15 mA until bromphenol blue migrated beyond the gel. Proteins were then electrotransferred (15) onto an Immobilon p15 membrane (Millipore Corp., Bedford, MA). The filters were blocked with 5% nonfat dry milk in 0.1% Tween 20 in PBS, then incubated overnight at 4°C with 1 μg/ml of primary antibody (anti-PARP or anti-actin as an internal standard for protein loading). The secondary antibody was horseradish peroxidase-conjugated anti-immunoglobulin (1:1000 in blocking solution). Controls to evaluate reactivity of proteins with secondary antibody alone were included. Bands were visualized with enhanced chemiluminescence reagent and subsequent exposure to hyperfilm-enhanced chemiluminescence (Amersham). Intensity of the bands was quantified by densitometric scanning (ScionScan 5000 USB densitometer; United States Biochemical, Cleveland, OH) and normalized with respect to actin. Controls loading increasing amounts of protein were included that confirmed the linearity of the densitometric measurements (data not shown). Because the 4C10-5 antibody recognizes the Mr 116,000 native PARP band and the Mr 90,000 PARP cleavage fragment, we estimate the percentage PARP cleavage as fol-
RESULTS

Time and Dose Dependence of PARP Cleavage in Human Colon Cancer Cell Lines. SW480 cells in logarithmic growth were incubated with 0.01, 0.1, 1, or 10 μM TPT or 20 μM CPT-11 for 24, 48, or 72 h. The time course and TPT dose response of the cleavage of PARP in SW480 cells, as measured by Western blotting, is shown in Fig. 1A. Fig. 1B shows the densitometric profile of these results. Western blot of the time course of PARP cleavage in response to 20 μM CPT-11 for 24, 48, or 72 h in SW480 cells and its densitometric profile are shown in Fig. 1C. Percentage PARP cleavage clearly increased with time of exposure and with elevated doses of the Topo I inhibitor. Only the M<sub>r</sub> 116,000 band corresponding to intact PARP protein and the M<sub>r</sub> 90,000 fragment typical of apoptotic cell death were visualized in all cells analyzed in tissue culture conditions.

Correlation between PARP Cleavage and Morphological Evidence of Apoptosis in Colon Cancer Cells Treated in Tissue Culture with TPT. In vitro experiments performed with HCT116, VACO5, VACO6, VACO8, VACO411, VACO425, and VACO451 colon cancer cell lines showed time and dose dependency of the cleavage of PARP in cells treated with TPT, as described for SW480 cells in Fig. 1. Fig. 2A shows control acridine orange-negative cells with homogeneous chromatin distribution. Fig. 2B shows the typical acridine orange conformation of apoptotic cells after treatment with 0.1 μM TPT for 48 h. The acridine orange-positive cells show chromatin condensation in apoptotic bodies, a hallmark of apoptotic cell death, and cell membrane blebbing. Fig. 2 shows a strong correlation between the percentage of PARP cleavage and percentage of apoptotic cells measured by acridine orange staining at 24 h (Fig. 2C) and 48 h (Fig. 2D). Nonparametric statistics were performed, resulting in Spearman correlation coefficient Rs: 0.88 (P < 0.005) and 0.91 (P < 0.002) at 24 and 48 h treatment with 0.1 μM TPT, respectively. We have chosen SW480 and VACO451 colon cancer cell lines to perform the in vivo experiments described below because of their location at the extremes of the curve, SW480 being among the most resistant and VACO451 among the most sensitive.

Growth Inhibition and PARP Cleavage in SW480 xenografts by TPT or CPT-11. The effects of TPT and CPT-11 on tumor growth and PARP cleavage were evaluated in athymic mice bearing SW480 (Fig. 3) and VACO451 (data not shown) colon cancer xenografts. Mice bearing SW480 xenografts were treated with increasing doses of TPT (1.25, 2.5, or 5 mg/kg) or CPT-11 (10 or 40 mg/kg) for five consecutive days. Fig. 3A shows the growth rate of xenografts in control and TPT-treated mice and PARP cleavage in xenografts assayed 24 h after completion of five daily sequential doses of TPT at the doses indicated. Results from Western blotting represent a portion of a xenograft (three different xenografts per treatment were analyzed). Fig. 3B shows the corresponding curve for CPT-11 treatment and PARP cleavage. The Topo I inhibitors clearly induced growth delay but not tumor regression. The results show that the maximum tumor response was already achieved with 1.25 mg/kg TPT or 10 mg/kg CPT-11 and was not improved by higher doses of either drug. In regard to the results of the percentage of PARP cleavage in these xenografts, some control samples showed a low degree of spontaneous PARP cleavage (0–5%). Results obtained by densitometric scanning from the Western blot in Fig. 3B show 12% PARP cleavage induced by 1.25 mg/kg TPT, 12% PARP cleavage induced by 2.5 mg/kg TPT, and 10% PARP cleavage induced by 5 mg/kg
Thus, the percentage of PARP cleavage was concomitant with the results of the growth curve, showing little or no differences between the three doses analyzed. Because the percentage PARP cleavage in vitro is associated with apoptosis or PCD, these results suggest that drug-induced growth delay is partially due to tumor cell death and repopulation rather than simple drug-induced inhibition of cell proliferation. Identical results were obtained in VACO451 xenografts under the same experimental conditions (data not shown).

Fig. 3C is an immunoblot showing the entire molecular weight range in different animals from the same experiment shown in Fig. 3B, corresponding to control, treatment with 5 mg/kg TPT, and treatment with 40 mg/kg CPT-11 showing 7, 10, and 6% PARP cleavage, respectively. Here we can evaluate PARP cleavage fragments with $M_i$ different than the $M_i$ 90,000 fragment described for apoptosis. Shah et al. (11) have detected smaller fragments at $M_i$ 50,000, 40,000, and 35,000 in HL-60 necrotic cells. As shown in Fig. 3C, in xenografts we have detected several bands reactive with the secondary antibody alone (anti-mouse IgG). The major bands were at $M_i$ 66,000–75,000, 50,000 and 25,000, whereas other minor bands were sometimes visualized at $M_i$ 55,000, 49,000, and 40,000. After incubation of the membrane with antibody to PARP, the $M_i$ 116,000 and 90,000 were visualized. Levels of the $M_i$ 90,000 fragment were proportional to tumor response. In the control sample, we also observed an $M_i$ 50,000 band reactive to PARP antibody that coincides with an IgG band.

Effect of TPT or CPT-11 on VRC5 Colon Cancer Xenografts. A more pronounced effect on PARP cleavage was shown in mice bearing the VRC5 human colon cancer xenografts that was shown previously to undergo tumor regression in response to treatment with Topo I inhibitors (30). Drugs were
administered in three cycles of 5 days, each separated by 2 days of rest. Treatment on days 1–5 was referred to as cycle 1, on days 8–12 referred to as cycle 2, and on days 15–19 referred to as cycle 3. Results shown in Fig. 4, A and B, indicate that treatment of VRC5 xenografts with TPT (2.5 mg/kg) induced a delay of tumor growth. Between days 13 and 23, the size of the tumor regressed modestly by about 100 mm³ before resuming growth between days 27–30. In contrast, treatment with CPT-11 (20 mg/kg) induced about 40% regression of tumors by the end of cycle 3 (Fig. 4B), when the drug was administered daily in the same three cycles described above. ig. 4B also shows PARP cleavage measured by Western blotting in one VRC5 xenograft per treatment in samples resected 24 h after the second and third 5-day cycles. Although baseline levels of PARP cleavage were observed in some control samples, increased PARP cleavage was evident in all treated samples compared with the controls. Treatment with TPT induced 13% PARP cleavage by the end of the second cycle and 20% PARP cleavage by the end of the third cycle, evaluated in samples shown in Fig. 4B. These results are similar to those observed in other animals (Fig. 4C) of the same experiment showing 28% PARP cleavage. Although at these times the tumors were about three times larger than at the start of treatment, they were in a regression phase compared with their size only 3 days earlier. Thus, the results and implications are similar to those observed with TPT treatment of the SW480 xenograft. The VRC5 tumor treated with CPT-11 showed 39% PARP cleavage after the second cycle of therapy and 28% PARP cleavage after the third cycle, evaluated from the Western blot shown in Fig. 4B. Results from another animal in the same experiment (Fig. 4C) show 37% PARP cleavage after the third cycle. These higher levels of PARP cleavage occurred under conditions where the tumor showed regression to 30–40% of their original size (Fig. 4B). The same molecular weight bands reactive with the secondary antibody alone (anti-mouse IgG) in SW480 xenografts (Fig. 3C) were observed in VRC5 xenografts. Apparently, the Mr 116,000 and 90,000 PARP fragments appear to be the main fragments generated by treatment with the Topo I inhibitors. An Mr 50,000 fragment was observed in some samples independent of treatment. Because the later observation occur in both treated and untreated tumors, it may represent some degree of spontaneous necrosis, as discussed below.

**PARP Cleavage in Colon Cancer Biopsies from Patients Treated with CPT-11.** Pre- and posttreatment samples from patients treated with CPT-11 were subjected to analysis by Western blotting to detect cleavage of PARP as described in “Materials and Methods.” Fig. 5A shows cleavage of PARP in control (C) and treated (T) samples, where C represents samples

![Figure 3](http://example.com/fig3.png)
obtained immediately before the start of treatment and $T$ represents samples from the same patient 24 h after initiation of treatment. Various levels of PARP cleavage were observed, from undetectable PARP cleavage in patient number 1, slight cleavage after treatment in patients numbers 2 and 3, and marked increase in PARP cleavage in patient number 4. Fig. 5B shows the entire molecular weight range of an immunoblot from patient 4 to assess the presence of PARP cleavage fragments typical of necrosis. The same major bands ($M_r 66,000–75,000$ and $50,000$) reactive with the secondary antibody alone (anti-mouse IgG) in SW480 and VRC5 xenografts (Figs. 3C and 4C) were also observed but at a much lower intensity because longer exposure time with the hyperfilm was required to reach similar intensity. These results clearly demonstrate the feasibility of detecting PARP cleavage in human tumors samples 24 h after chemotherapy with Topo I inhibitor. Additional studies will be required to determine the association between levels of PARP cleavage and clinical response to treatment.

**DISCUSSION**

This study demonstrates that PARP cleavage occurs *in vitro* and *in vivo* in colon cancer responding to treatment with camptothecins. Results in this report confirm that PARP cleavage is a useful marker to assess PCD in colon cancer cell lines in tissue culture conditions. Interestingly, the same cancer cells can respond differently in culture or *in vivo*, as shown for SW480 and VACO451 colon cancer cells, responding similarly when grown as xenografts *in vivo* but being among the least and most sensitive, respectively, when grown in tissue culture (Fig. 2). Although Topo I inhibitors have been shown to be effective chemotherapeutic agents against human colon cancer, their efficacy rate against cells growing in tissue culture or as xenografts in athymic mice is greater than their efficacy against solid colon tumor growth in patients. In fact, the clinical response rate in such patients is estimated at $7–32\%$, depending on the agent used, dose, and schedule of administration (34, 35). These agents are also capable of producing significant toxicity, especially myelosuppression and diarrhea. It would therefore be useful to have an early predictor for response to Topo I-based chemotherapy to determine whether to continue use of these agents or to stop them to try an alternative regimen.

The demonstrations that Topo I inhibitors induce PCD in colon cancer cells that can be quantitated by PARP cleavage provide the potential basis for early evaluation of response to Topo I inhibitors *in vivo*. In this study, we show in a series of colon cancer cell lines *in vitro* that PARP cleavage is proportional to apoptosis induced by Topo I inhibitors. We subsequently show in human colon cancer xenografts growing in athymic mice that PARP cleavage is induced in tumors undergoing stabilization and regression in response to systemic ad-

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**Fig. 4** Effect of TPT or CPT-11 in VRC5 colon cancer xenografts. A, growth rate expressed in tumor volumes (mm$^3$) as a function of time. Xenografts were measured every other day, and tumor volume was estimated as described in “Materials and Methods.” B, relative growth rate expressed as arbitrary units considering size of tumors at beginning of treatment as one (1). PARP cleavage measured by Western blotting in VRC5 xenografts after treatment with 2.5 mg/kg TPT or 20 mg/kg CPT-11 24 h after cycles 2 and 3. C, immunoblot showing the entire molecular weight range.
both apoptotic and necrotic cell death occur with PARP cleavage; nevertheless, the pattern of cleavage differs (11). Apoptotic cell death results in PARP fragments of $M_r$ at about 90,000 and 26,000, whereas it has been reported that during necrosis, further cleavage of PARP occurs, and smaller fragments at $M_r$ 50,000, 40,000, and 35,000 can be observed (11). In our studies, two major bands at $M_r$ 66,000–75,000 and 50,000 and other minor bands at $M_r$ 55,000, 49,000, and 25,000 result from reactivity to anti-IgG (secondary antibody) in tissue samples. The $M_r$ 50,000 band corresponding to IgG fall in the same area where the PARP fragment $M_r$ 50,000 corresponding to necrotic death should be found. Nevertheless, it appears that only the $M_r$ 90,000 fragment can be observed after treatment with Topo I inhibitors in the tumor samples analyzed because little increase in the $M_r$ 50,000 band was observed. Furthermore, in addition to the effect of cell death induced by the Topo I inhibitors, other types of cell death intrinsic to the tumor may occur. Included in this latter type of cell death is necrotic death produced by hypoxia (36), which may explain the appearance of the $M_r$ 50,000 fragment detected in the control sample of SW480 xenograft shown in Fig. 3C.

The increases in PARP cleavage that occur in tumors that undergo shrinkage in response to Topo I inhibitors appear to be associated with tumor cell death. PARP cleavage occurs as well in tumors, the growth of which are stabilized in response to Topo I inhibitors, although the percentage of PARP cleavage in the stabilized tumors is less than that which occurs in the regressing tumors. This observation suggests that stable tumor size may reflect a balanced process of tumor cell death and tumor cell proliferation. Nonetheless, in both model situations where tumors remain stable or regress, the responses to treatment with Topo I inhibitors were reflected by an increase in PARP cleavage.

In these studies on patients with metastatic colon cancer undergoing therapy with a 90-min infusion of CPT-11, we performed tumor biopsies before and 24 h after the first course of chemotherapy. Although the optimal time after therapy to biopsy human tumors is unclear to show PARP cleavage, we selected the 24-h point because it was more convenient and readily accepted by patients to have the procedure performed as part of a single visit and evaluation process including pretherapy biopsy, therapy, drawing blood samples for pharmacokinetic studies, followed by a 24-h posttherapy CT-guided biopsy. Although it is possible that biopsies at later times might show a greater amount of PARP cleavage, our present results demonstrate that PARP cleavage can be clearly demonstrated at 24 h after therapy in a series of patients undergoing 90-min CPT-11 infusion. The possibility that measurements of apoptosis may be useful to predict therapeutic outcomes has been considered previously (37, 38). Our observations provide the basis for a clinical trial to determine whether PARP cleavage assay can be correlated with standard clinical parameters of chemotherapy response and whether the percentage of PARP cleavage will correlate with the degree and/or duration of clinical response.

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