**DNA Damage Persistence as Determinant of Tumor Sensitivity to the Combination of Topo I Inhibitors and Telomere-Targeting Agents**

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**Abstract**

**Purpose:** We previously reported that the G-quadruplex (G4) ligand RHPS4 potentiates the antitumor activity of camptothecins both in vitro and in tumor xenografts. The present study aims at investigating the mechanisms involved in this specific drug interaction.

**Experimental Design:** Combination index test was used to evaluate the interaction between G4 ligands and standard or novel Topo I inhibitors. Chromatin immunoprecipitation was performed to study the presence at telomeres of various types of topoisomerase, while immunolabeling experiments were performed to measure the activation of DNA damage both in vitro and in tumor xenografts.

**Results:** We report that integration of the Topo I inhibitor SN-38, but not the Topo II poison doxorubicin with telomere-based therapy is strongly effective and the sequence of drug administration is critical in determining the synergistic interaction, impairing the cell ability to recover from drug-induced cytotoxicity. The synergistic effect of this combination was also observed by using novel camptothecins and, more interestingly, mice treated with ST1481/RHPS4 combination showed an inhibition and delay of tumor growth as well as an increased survival. The study of the mechanism(s) revealed that treatment with G4 ligands increased Topo I at the telomeres and the functional relevance of this observation was directly assessed by showing that standard and novel camptothecins stabilized DNA damage both in vitro and in xenografts.

**Conclusions:** Our results demonstrate an outstanding efficacy of Topo I inhibitors/G4 ligands combination, which likely reflects an enhanced and persistent activation of DNA damage response as a critical determinant of the therapeutic improvement.

**Introduction**

Guanine-rich stretches of DNA have a high propensity to self-associate into planar guanine quartets to give unusual structures (1) called G-quadruplexes (G4). Quadruplexes are thought to play important roles in some biological events because many guanine-rich regulative regions in the human genome possess the potential to adopt a quadruplex conformation. The conformations of G4 provide selective recognition sites for small molecules and thus these structures have become important drug-design targets for the treatment of various human disorders. Two drugs acting on nucleolin that either target a G4 (CX-3543 or Quarfloxin) or fold into a G4 structure (AS1411) are in Phase II clinical trials against cancer (2, 3).

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Translational Relevance

Telomere pathway is a well-validated target at the preclinical level, encouraging the evaluation of therapeutic combined option in future clinical protocols. In this context, we have recently reported a specific link between the telomere-targeting agent RHPS4 and chemosensitivity toward camptothecins in colorectal tumors.

The present study strongly supports the use of this combination in cancer therapy by demonstrating a synergistic effect between telomere-targeting agents and novel clinical-relevant camptothecins, having antitumor activity in a large panel of human tumors and favorable pharmacodynamic and pharmacokinetics properties.

We also showed that stabilization of DNA damage, evaluated by induction and persistence of γH2AX foci, is a key determinant in the sensitivity to this combination therapy. In conclusion our results show an improvement of the therapeutic efficacy of Topo I inhibitors in combination with G4 ligands and identify γH2AX formation as a useful biomarker for monitoring the efficacy of this combination in future clinical applications.

telomerase reaction and G4 formation has been shown to inhibit telomere elongation in vitro (9).

In human cells, the complete replication of telomeric DNA usually depends on telomerase, a specialized reverse transcriptase that uses its RNA template to add G-rich telomeric repeats to the terminal 3' overhang (10). In preclinical studies, telomerase inhibitors have shown promise as effective antitumor agents against a variety of human tumors. These translational advances have resulted in the first antitelomerase agent, the oligonucleotide-based GRN163L targeting the telomerase RNA template, completing Phase I/II clinical studies (11).

The inability of telomerase to utilize a G4 folded telomeric substrate has led to the emergence of a novel strategy for cancer therapy. G4-interacting agents are small molecules able to bind and stabilize the telomeric DNA in a quadruplex conformation, thereby inhibiting telomere extension by telomerase (12). Interestingly, G4-interacting compounds might disrupt telomere architecture, both in telomerase- and ALT-positive tumors, causing immediate and profound effects on cell proliferation (13). Over the past decade, many chemical classes of G4 ligands have been described. Several of them reduce the growth of various cancer cell lines in vitro, often accompanied by cellular senescence and/or apoptosis, and can be considered as telomere-damage inducers as evidenced by the characteristic DNA damage response (i.e., the appearance of γH2AX foci) at the telomeres. Moreover, some of them exhibit antitumoral activity in mice bearing various human tumor xenografts (14–17). It is encouraging for future clinical applications that several G4 ligands show in vivo synergistic activity with some conventional cytotoxic agents (18–21).

RHPS4 (3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate) is one of the most effective and selective G4 ligands. Our previous studies revealed that this agent, by stabilizing G4 DNA at telomeres, impairs fork progression and/or telomere processing resulting in telomere damages (16, 22). Telomere dysfunction is the major cause of RHPS4 toxicity since POT1 or TRF2 overexpression is sufficient to overcome the deleterious effects of RHPS4 on cellular proliferation and DNA damage (16). In agreement with the view that the telomere specific effects of RHPS4 is due to G4 stabilization, RHPS4 selectivity binds to quadruplex vs. duplex DNA (23). Interestingly in view of clinical application, RHPS4 is active in vivo as a single agent with a good toxicological profile (16, 20).

Telomeric binding proteins facilitate the relief of the topological stress occurring during the progression of the replication fork (24), suggesting that drugs that inhibit topoisomerase activity, which are widely used in the therapy of different types of cancer, might synergize with antitelomere strategies. Camptothecins are topoisomerase I (Topo I) inhibitor chemotherapeutic agents and analogs such as irinotecan and topotecan are approved for treatment of many types of solid tumors such as lung, colorectal, ovarian, cervical, and gastric carcinomas. Unfortunately they are not curative as single agents. To improve the efficacy of Topo I inhibitors several approaches could be pursued including development of new camptothecins with a more favorable therapeutic profile and their combination with other cytotoxic agents and/or molecularly targeted agents, on the basis of the knowledge of the mechanisms of tumor cells response (25). The convergence of these efforts could result in more effective anticancer therapies.

In this context, we recently reported that antitumor efficacy of camptothecins is increased when used in combination with the G4 ligand RHPS4 (20). On the basis of these results, the aim of the present study was to investigate the mechanism(s) involved in this specific drug interaction by using well-characterized G4 ligands and standard or novel Topo I inhibitors (26–29).

Materials and Methods

Drugs

7-Ethyl-10-hydroxycamptothecin (SN-38, Alexis) and adriamycin (Adriblastina, Pharmacia) were used. ST1481 (Gimatecan), ST1968 (Namitecan) camptothecins (30, 31) were provided by Sigma-Tau. IDN5174 was supplied by INDENA. The G4 ligands RHPS4, CORON, and PIP-PIPER (1, 7) were synthesized as previously described (23, 32).

Cell lines and culture conditions

BJ fibroblasts expressing hTERT and SV40 early region (BJ-HELT) were maintained as previously described (33). HT29 and HCT116 colorectal adenocarcinoma cells were obtained and maintained as previously reported (20).
Cytotoxic assay

Cells were seeded at a density of $5 \times 10^6$ cells/plate and exposed 24 hours later to the following drugs: RHP54 (0.5–2 μmol/L for 96 hours); CORON (0.01–0.1 μmol/L for 96 hours); PIP-PIPER (1, 7) (1–10 μmol/L for 96 hours); SN-38 (0.5–2 μmol/L for 2 hours); ST1481 (0.01–0.1 μmol/L for 2 hours); IDN5174 (0.5–10 μmol/L for 2 hours) and ST1968 (0.1–5 μmol/L for 2 hours). In the combination experiments, the medium containing the first drug was removed and replaced with fresh medium containing the second drug. Colony forming ability was evaluated as previously reported (34).

Chromatin immunoprecipitation assay

BJ-HELT fibroblasts were treated for 24 hours with 0.5 μmol/L RHP54, 0.05 μmol/L CORON, and 4 μmol/L PIP-PIPER (1, 7), or for 2 hours with 0.5 μmol/L SN-38. Chromatin immunoprecipitation (ChIP) assay was performed as previously described (16). The following antibodies were used: pAbs anti-Topo I, Topo IIα, and Topo IIIα (Abcam). mAb anti-β-actin (Sigma Chemicals) was used as negative control of the ChIP assay.

Immunofluorescence analysis

BJ-HELT fibroblasts were treated with 0.5 μmol/L SN-38 for 2 hours and 0.5 μmol/L RHP54 for 48 hours alone or in combination. Cells were processed for immunofluorescence (IF) as previously reported (22) using the following antibodies: mAb anti-γH2AX (Upstate) and pAb anti-TRF1 (Abcam). To estimate the percentage of γH2AX-positive cells and the percentage of cells containing at least 4 γH2AX/TRF1 colocalizations (TIF, Telomere-dysfunction-Induced Foci), at least 200 nuclei or 50 nuclei for each sample, respectively, were scored.

Cell cycle analysis and apoptosis

Cell cycle analysis was performed by flow cytometry (Becton-Dickinson) as previously reported (34). Apoptotic cells were scored by Hoechst staining.

Antitumor activity

CD-1 male nude (nu/nu) mice, 6 to 8 weeks old were purchased from Charles River Laboratories. All procedures involving animals and their care were conducted as previously reported (35). RHP54 was given i.v. at 10 mg/Kg/d for 15 consecutive days and ST1481 was administered per os at 1.5 mg/kg every 4 days for 4 times, based on previous results (20, 36). In particular, nude mice were injected with HT29 at $3 \times 10^6$ cells/mice and treatments were started when a tumor mass of about 600 mg was evident in the mice. In the combination experiments the 2 drugs were administered with an interval of 24 hours. The tumor weight was calculated from caliper measurements (37) and antitumor efficacy of treatments was assessed as previously reported (20).

Immunohistochemical analysis

Activation of damage response was determined immunohistochemically by using mAb anti-γH2AX (Upstate) as previously reported (16). The number of γH2AX-positive cells were counted in 8 high-power fields (400× magnification) per section and reported as γH2AX-positive nuclei/mm². Two independent observers did the counts in blinded fashion.

Statistical analysis

Synergism, additivity, and antagonism were assessed by isobologram analysis using the Chou–Talalay method as previously described (20). Combination index (CI) values <0.9, >0.9 and <1.2, >1.2 indicate synergism, additive effect, and antagonism, respectively. Student's t-test (unpaired, 2-tailed) was used for statistical comparison of differences. Survival curves of mice were generated by Kaplan–Maier product-limit estimate, and statistical differences between the various groups were evaluated by log-rank analysis with Yates correction (software Primer of Biostatistics; McGraw-Hill). Differences were considered statistically significant when $P < 0.05$.

Results

The Topo I inhibitor SN-38 and telomere-targeting agents in combination have a strong synergistic effect

Previous data of combined treatment between the G4 ligand RHP54 and a classic topoisomerase inhibitor revealed a good synergism between these compounds both in vitro and in xenografts (ref. 20 and Fig. 1A). The present study aims at investigating the mechanisms involved in this specific interaction. Firstly, we evaluated the efficacy of SN-38 with well-established telomere targeting agents. The exposure of HT29 colon carcinoma cells to the combination of SN-38 and the G4 compounds RHP54, CORON, and PIP-PIPER (1, 7) strongly reduced cell survival (Fig. 1A). These results reported in terms of CI showed a synergistic interaction (as documented by CI values less than 0.1), when cells were treated with SN-38 followed by G4 ligands (Fig. 1B). The sequence-dependent effect of this combination was highlighted by a slight additive or antagonistic effect observed by treating the cells with the opposite sequence of drug treatment (Fig. 1B). The positive interaction between SN-38 and telomere-targeting agents seems to be specific for the Topo I inhibitor, since the combination with the Topo II inhibitor doxorubicin did not show a marked increase of cytotoxic activity and the effect was almost additive or antagonist regardless of the G4 ligands and/or the sequence of drug treatment (Fig. 1C and D).

Analysis of cell cycle perturbation and cell death strongly supported the sequence-dependent effect of the SN-38/G4 ligands combination. SN-38 alone induced a block of cells in S-phase that was almost recovered at 48 hours after the end of treatment (Fig. 2A). A similar cell cycle profile was observed in the RHP54 → SN-38 combination, demonstrating that the treatment with RHP54 before the Topo I inhibitor caused a decrease of cells in S-phase that remained lower than the control at 48 hours. The Topo I inhibitor strongly hindered the recovery of the cell cycle profile, as shown in Figure 2B. In addition, we investigated the effect of the combination treatment on cell viability in HT29 cells. The Cytotoxic assay showed a marked decrease of cell viability when the drugs were administered in combination. In particular, a marked reduction of cell viability was observed when SN-38 was administered before the Topo I inhibitor, as shown in Figure 2C.
inhibitor did not impair the ability of cells to recover from drug-induced S-phase arrest (Fig. 2A). Interestingly, cells exposed to the SN-38 RHPS4 combination still showed a strong perturbation of cell cycle and a significant amount of cells were in the sub-G1 compartment (Fig. 2A). Quantitative analysis of cell death by Hoechst staining, revealed that about 30% of cells showed apoptotic bodies in the SN-38 RHPS4 combination, percentage that was less of 10% in the opposite sequence as well as in the SN-38 alone (Fig. 2B and C). Our results suggest that the sequential combination of SN-38 with G4 ligands impairs the cells to recover from drug-induced cytotoxicity.

Treatment with G4 ligands increases the amount of Topo I at telomeres
To understand the molecular basis of the positive interaction between a Topo I inhibitor and telomere-targeting agents, we investigated the ability of different G4 ligands to modulate the topoisomerase binding to telomeric DNA. Chromatin Immunoprecipitation assay performed in BJ-EHLT fibroblasts showed an enrichment of Topo I at the telomeric sequences in the samples treated with RHPS4, CORON and PIP-PIPER (1, 7) compared to untreated ones. This enrichment was not observed by using the Alu probe (Fig. 3A and C), thus indicating a specific recruitment of Topo I at telomeres. As control of this result, increased amount of Topo I at both telomeric and Alu sequences was found in cells exposed to the Topo I inhibitor SN-38 (Fig. 3B and D).

The binding to telomeric DNA of Topo IIIb, a topoisomerase of Topo I family, was also increased in RHPS4-treated sample (Fig. 3A), consistently with the ability of this G4 ligand to activate the Bloom syndrome helicase (BLM; 22). In agreement with previous studies (24), we detected the presence of Topo IIIb at the telomeres of untreated cells. However, in contrast to Topo I, we did not observe any enrichment of Topo IIIb at telomeric regions. We conclude that G4 ligands trigger a DNA damage that...
specifically requires the Topo I, providing an explanation for the strong synergistic interaction we observed between G4 ligands and camptothecin.

Combined treatment of SN-38 and RHPS4 causes a persistent DNA damage

By means of the phosphorylation of H2AX (γH2AX) as a sensitive hallmark of DNA damage, we found that the percentage of γH2AX-positive cells was significantly increased after SN-38 and RHPS4 exposure (Fig. 4A). Interestingly, cells treated with SN-38 alone rapidly recovered the damage, the percentage of γH2AX-positive cells decreased from about 70% to 30% at 48 hours after the end of treatment (Fig. 4A). This finding is consistent with the reversibility of the camptothecin-mediated DNA damage. When SN-38 was followed by RHPS4 treatment, cells failed to recover the DNA damage, and the percentage of damaged cells remained significantly higher if compared to that of SN-38 or RHPS4 alone (Fig. 4A). Of note, the treatment with RHPS4 before SN-38 did not impair the capacity of cells to recover the damage (Fig. 4A), consistently with the observation showing that this sequence of drug exposure did not elicit a synergistic interaction (ref. 20 and this paper). About 60% of the γH2AX foci remained 48 hours after the end of treatment in SN-38 → RHPS4 combination, while the opposite sequence allowed to reduce the number of DNA damage foci to 10% (Fig. 4B). Analysis of telomeric DNA damage by measure the percentage of cells showing more than 4 colocalizations between γH2AX and the telomeric marker TRF1 (TIF-positive cells) as well as the average number of TIFs, revealed that SN-38 induced telomere damage in almost the totality of damaged cells that was stabilized in the SN-38 → RHPS4 combination (Fig. 4C–E).

Our results clearly demonstrate that the DNA damages elicited by G4 ligands cannot be efficiently repaired in camptothecin-treated cells.

Novel camptothecins and RHPS4 combination limits the growth of colon cancer cells both in vitro and in xenografts: use of γH2AX as marker of tumor response

We finally evaluated the interaction between the G4 ligand RHPS4 and 3 novel camptothecins with a more
favorable therapeutic and pharmacological profile than clinically used camptothecins, including IDN5174, ST1968, and ST1481. As reported in Figure 5A, the treatment with camptothecins followed by RHPS4 was highly effective as revealed by the reduction of survival of HT29 cells by 1 to 3 order of magnitude, depending on the camptothecin used. Again, this effect was markedly dependent on the sequence employed, since the opposite sequence of treatment produced only a slight reduction of clonogenic ability. The results have been confirmed in another coloncarcinoma line (Fig. 5B) and the analysis of these data by using the CI confirmed that the optimal sequence has a strong synergistic effect on cell survival (Fig. 5C and D).

Based on in vitro results, experiments were performed in vivo on HT29 tumor-bearing mice. In particular, we focused our attention to the combination of RHPS4 with ST1481, an orally bioavailable camptothecin currently undergoing clinical trials. ST1481 confirmed its relevant antitumor efficacy, being tumor weight significantly reduced ($P < 0.001$) compared to any single treatment groups (Fig. 6A and Supplementary Table SI). Of note, a further improved antitumor efficacy has been observed when a second cycle of treatment was administered. Mice receiving 2 cycles of treatment had a significant advantage ($P < 0.001$) in terms of reduction of tumor mass and this effect persisted for almost 2 months (55 days of tumor growth delay and nearly 100% complete response rate in 7 of 8 mice). This marked and prolonged antitumor effect produced an impressive increase in overall mice survival of 269% that was significantly different ($P < 0.001$) to all other treatment groups (Fig. 6B and Supplementary Table SI).

To verify if activation of damage response can be used as surrogate marker of tumor response, immunohystochemical analysis of $\gamma$H2AX was performed in tumor specimens. ST1481 markedly increased the $\gamma$H2AX staining, the number of positive nuclei/mm$^2$ increased of about 8-fold compared to untreated. The number of $\gamma$H2AX-positive cells was significantly ($P = 0.003$) reduced up to 50% 1 week after the end of ST1481 treatment, while it was still high when ST1481 was followed by RHPS4 administration.

Our results demonstrate the high therapeutic efficacy of ST1481/RHPS4 combination suggesting that persistent activation of DNA damage response is a key determinant of the antitumor effect.
Discussion

Stabilization of telomeric G4 can be considered an original strategy for controlling tumor growth, making G4 ligands attractive potential anticancer agents (38). We recently showed that one of them, the RHPS4 molecule, has an antitumor effect, by selectively inducing telomere damage in xenografted tumor models. More recently, we have uncovered a specific link between RHPS4 and chemosensitivity toward camptothecins in colorectal tumors. In the present study we have investigated the mechanism(s) involved in this specific drug interaction.

We confirmed the strong synergistic interaction between camptothecin and RHPS4 by using other G4 ligands and novel camptothecin analogues, clearly demonstrating that the synergistic effect between Topo I inhibitors and telomere-targeting agents is a general phenomenon. These results have been obtained by using cytotoxic doses of camptothecins, able to reduce cell viability and induce DNA damage, and therefore they are reasonably ascribed to Topo I-mediated effects.

Strikingly, the best synergistic drug interaction is observed if camptothecins are given before G4 ligands. Thus, camptothecin-treated cells are either more prone to be damaged by RHPS4 or less efficient to repair RHPS4-dependent damages or both. In favor of the second possibility, we did not observe an increased rate of damage due to RHPS4 in camptothecin-treated cells but rather a persistence of the damage. This suggests that Topo I is normally required to repair the telomeric damages elicited by G4-ligands and that its inactivation by camptothecin prevents or impairs this repair. In agreement with this hypothesis, we found that Topo I is enriched at telomeres of RHPS4-treated cells. This unveils a function of Topo I at telomeres in relation with G4 formation. These results, together with in vitro results showing that Topo I binds to G4 tetraplexes (39) and functionally interacts with the Werner helicase (40) that unwinds these DNA structures (41), suggest that in vivo Topo I resolves the G4 tetraplexes that either occur during the transcription, replication, or recombination of telomeric DNA or are the outcome of G4 stabilizing agents. Whether this function of Topo I involves its DNA relaxation

Figure 4. Stabilization of DNA damage in SN-38 + RHPS4 combination. BJ-EHLT fibroblasts were treated with 0.5 μmol/L SN-38 for 2 hours or 0.5 μmol/L RHPS4 for 48 hours. In the combination experiments, the medium containing the first drug was removed and replaced with fresh medium in presence or absence of the second drug. Cells were processed for IF using antibodies against γH2AX and TRF1 to mark telomerers.

Percentage of γH2AX- (A) and TIF-positive cells (C) in untreated (−) and cells exposed to the indicated treatments. Cells with 4 or more γH2AX/TRF1 foci were scored as TIF positive. Analysis was performed from 12 to 48 hours after the end of treatments. Average number of γH2AX (B) and γH2AX/TRF1 (D) foci in the indicated samples. The mean of 4 independent experiments with comparable results is shown. Error bars indicate ± SD. P values are *, P < 0.05 and **, P < 0.01. E, representative images of IF in the indicated samples acquired with a Leica Deconvolution microscope (magnification 100×) are reported.
activity or other of its functions (42) remains to be further explore.

These results suggest a key role of Topo I on telomere-based therapy and demonstrate that combination of SN38 with G4 ligands makes cells unable to recover from drug-induced cytotoxicity. Impressively, mice treated with ST1481/RHPS4 combination showed an inhibition and delay of tumor growth and an increased survival. This is particularly relevant from a clinical point of view, since ST1481 has completed phase II clinical trial in advanced ovarian cancers showing activity and a manageable safety profile (29). Analysis of damage response in vivo by measuring the γH2AX-positive cells in the tumor samples upon the different treatments, revealed that while the number of γH2AX-positive cells was reduced 4 days after the end of ST1481 treatment, it was still high when ST1481 was followed by RHPS4 administration.

In conclusion, our studies provide a compelling argument to suggest that the integration of G4 ligands to camptothecin-based treatment might be a highly valuable therapeutic combination. Assaying for the persistence of DNA damage response in tumor might be used as a surrogate marker of tumor response.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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