Targeting Topoisomerase I in the Era of Precision Medicine
Anish Thomas and Yves Pommier

Abstract

Irinotecan and topotecan have been widely used as anticancer drugs for the past 20 years. Because of their selectivity as topoisomerase I (TOP1) inhibitors that trap TOP1 cleavage complexes, camptothecins are also widely used to elucidate the DNA repair pathways associated with DNA–protein cross-links and replication stress. This review summarizes the basic molecular mechanisms of action of TOP1 inhibitors, their current use, and limitations as anticancer agents. We introduce new therapeutic strategies based on novel TOP1 inhibitor chemical scaffolds including the indenoisoquinolines LMP400 (indotecan), LMP776 (indimitecan), and LMP744, and on tumor-targeted delivery TOP1 inhibitors using liposome, PEGylation, and antibody–drug conjugates. We also address how tumor-specific determinants such as homologous recombination defects (HRD and BRCAness) and Schafen 11 (SLFN11) expression can be used to guide clinical application of TOP1 inhibitors in combination with DNA damage response inhibitors including PARP, ATR, CHEK1, and ATM inhibitors.

Introduction

Humans encodes six topoisomerases, TOP1, TOP1MT, TOP2a, TOP2β, TOP3a, and TOP3β (1) to pack and unpack the approximately 2 meters of DNA that needs to be contained in the nucleus whose diameter (6 μm) is approximately 3 million times smaller. Moreover, the genome is organized in chromosome loops and the separation of the two strands of DNA during transcription and replication generates torsional stress and supercoils that are resolved by topoisomerases.

While TOP1, like all six human topoisomerases removes DNA negative supercoiling (underwinding), only TOP2α and TOP2β resolve DNA knots and intertwined DNA circles (decatenation) as they cleave both DNA strands. While TOP3α resolves hemicatenate and double-Holiday junctions, only TOP3β acts as RNA topoisomerase (1). In all cases, topoisomerases change the topological state of nucleic acids by forming topoisomerase cleavage complexes (TOPCC) that enable an intact DNA or RNA to pass through the topoisomerase-linked breaks made in the DNA (or RNA for TOP3β). The normal activity of topoisomerases relies on the fact that, following topoisomerization, TOPCCs reverse rapidly by the religation of the broken DNA or RNA, which releases the topoisomerase. TOP1 is essential in vertebrates where it is required for genomic stability and for removing both positive and negative DNA supercoils that otherwise lead to the formation of alternate DNA structures such as plectonemes, guanosine quartets, R-loops, and DNA breaks (reviewed in ref. 1).

Anticancer TOP1 Inhibitors Trap TOP1CCs as Interfacial Inhibitors

The plant alkaloid camptothecin and its clinical derivatives, topotecan and irinotecan (Fig. 1A, right) target TOP1CCs by binding at the interface of TOP1CCs (Fig. 1B). They do not bind DNA without TOP1 or TOP1 without DNA, and the binding is stereospecific for the natural camptothecin 20-S isomer (Fig. 1B). Cocrystal studies (ref. 2; Fig. 1B) showed that TOP1CCs are trapped by the reversible binding of a single camptothecin molecule resulting from: (i) stacking of the polycyclic ring scaffold of the drug against the base pairs flanking the DNA nick made by TOP1, and (ii) a network of hydrogen bonds between camptothecin and Asn722, Arg364, and Asp533 of TOP1. Hence camptothecins block the religation of TOP1CCs as archetypal interfacial inhibitors (3). The non-camptothecin indenoisoquinolines in clinical development (Fig. 1A, left; see below) also act by binding at the TOP1–DNA interface (Fig. 1B) and trapping TOP1CCs (4, 5).

Determinants of Response and Pharmacogenomic Signature for TOP1 Inhibitors: TOP1, Replication, HRD, ATR, PARP, and SLFN11

Consistent with the trapping mechanism, TOP1 (Fig. 1B) is required for cell killing by camptothecins with total resistance in Top1-knockout yeast and increased sensitivity by overexpression of TOP1 (6, 7). Moreover, supporting the selective targeting of TOP1 by camptothecins, mutations of TOP1 confer resistance to camptothecins in cancer cells (8). Yet, TOP1CC levels are not sufficient for cellular response (9), and replication fork collisions are a major determinant of cell killing (Fig. 1C; ref. 1). In the absence of replication (and transcription), trapped TOP1CCs...
Figure 1.
Outline of the molecular pharmacology and response determinants of clinical TOP1 inhibitors. A, Chemical structures of the camptothecin derivatives used in the clinic. R1, R2, and R3 refer to the positions of substitutions that confer water solubility to irinotecan and topotecan. Camptothecins are active in lactone form and are readily inactivated at physiologic pH in the blood and tissues by E-ring hydrolysis to their ring-open carboxylate form (top right), which is sequestered by serum albumin (right). The clinical indenoisoquinoline derivatives, LMP400, LMP776, and LMP744 (left). B, Both the camptothecins and indenoisoquinolines trap TOP1CCs by binding at the enzyme–DNA interface. C, Replication damage induced by TOP1 inhibitors. D, Collision of a replication fork with a TOP1CC on the leading strand for DNA synthesis generates a single-ended DNA double-strand break (DSE: double-stranded end) by replication run-off. E, Alternatively, the colliding fork can be remodeled by replication fork reversal (promoted by HLTF, ZRANB3, SMARCL1, RAD51, and PCNA polyubiquitylation) which may convert the TOP1CC to a potentially reversible configuration. Fork restart is promoted by the helicase RecQ1 and the MCM10 replication helicase. PARylation of RecQ1 prevents its activity and thereby keep forks in the reversed configuration. (Continued on the following page.)
Collisions of transcription and replication with trapped TOP1CCs induce the degradation of TOP1 by the ubiquitin proteasome pathway and as a result of ATR and HR by irreversibly blocking replication and HDR (28, 29).

Because response and resistance determinants to TOP1 inhibitors are multifactorial in preclinical models, it is likely that pharmacogenomic signatures will have to be implemented to improve the clinical use of TOP1 inhibitors. Translational signature determinants are beginning to be identified. They include SLFN11, BRCAness/HRD, and ABCG2. Additional factors remain to be identified, and cancer cell line databases and synthetic lethality screens with TOP1 inhibitors are approaches to achieve this goal (26).

Approved TOP1 Inhibitors and Their Limitations

The first camptothecin clinical trial was conducted in the early 1970’s (ref. 30; see Fig. 1A, right). In spite of objective responses, clinical trials were not pursued. Fifteen years later, the discovery of TOP1 as the target of camptothecins (31) brought water-soluble camptothecin derivatives back to the clinic, leading to the FDA approval of irinotecan and topotecan in 1996 (Table 1).

Irinotecan is a prodrug. It needs to be converted by carboxylesterases into its active metabolite, SN-38 (Fig. 1A). The pharmacokinetics of irinotecan and SN-38 depend on a pH-dependent equilibrium between the active lactone and inactive carboxylate forms (Fig. 1A; ref. 32). The plasma area under the concentration versus time curve (AUC) of SN-38 is 2%–8% of irinotecan, and SN-38 is 95% bound to plasma proteins (33). SN-38 levels peak at the end of infusion with a mean terminal half-life of approximately 10–20 hours. SN-38 is cleared via glucuronidation (SN-38G) and biliary excretion. A host of transporters are involved in its metabolic transformation, active transport, intestinal absorption, and hepatobiliary secretion (32, 34). Interindividual variability in pharmacogenomics results in marked heterogeneities in efficacy and toxicity of irinotecan.

The dose-limiting toxicities of irinotecan are myelosuppression and diarrhea, with an incidence of about 15%–20%. Early diarrhea within hours of administration is related to a cholineric surge from inhibition of acetylcholinesterase. Late diarrhea occurring after 24 hours is unpredictable and can be severe or life threatening in 23%–31% patients (33). Direct mucosal cytotoxicity from free intestinal luminal SN-38 or SN-38G deconjugation (by bacterial β-glucuronidase back to SN-38) underlies the late diarrhea. SN-38-induced apoptosis and hypoproliferation in the intestines causes colonic damage with changes in goblet cell morphology, and mucin secretion. Individuals who are homozygous for the UGT1A1*28 allele (10% of North Americans; UGT1A1 7/7 genotype) are also at increased risk for neutropenia (35).

Topotecan also undergoes reversible hydrolysis to the opening inactive carboxylate form (Fig. 1A), which predominates at physiologic pH (36). Topotecan’s terminal half-life is only 2–3 hours, which limits its efficacy because sustained drug exposure is needed to maintain the TOP1CCs until replication/transcription collisions lead to cell death (Fig. 1B and C). The
Table 1. Clinical indications, major toxicities, and clinical pharmacology of the FDA-approved camptothecins

| Compound          | Tumor type          | Clinical indication                                      | Major toxicities                        | Metabolism                                                                 | Elimination                                                                 |
|-------------------|---------------------|----------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Irinotecan        | Metastatic colorectal cancer | First-line in combination with 5-fluorouracil and leucovorin | Nausea, vomiting, diarrhea, myelosuppression | Prodrug that requires enzymatic cleavage of the C-10 side chain by an irinotecan carboxylesterase–converting enzyme to generate the active metabolite SN-38. Can also undergo hepatic oxidation of its dipiperidino side chain to form the inactive metabolite 7-ethyl-10-(4-N-(5-amino-1-piperidino)carbonyloxy)camptothecin. | About 16% (range, 11.1%–20.9%) excreted unchanged in urine. SN-38 is glucuronidated, and both the conjugated and unconjugated forms are excreted in the bile. |
| Topotecan         | Metastatic ovarian cancer | Recurrent disease following initial fluorouracil-based therapy | Myelosuppression | Nonenzymatic hydrolysis of the lactone ring generates the less active open-ring hydroxy carbocyclic acid. N-desmethyl is a minor metabolite. | About 26%–41% excreted unchanged in urine over 24 hours. Concentrated in the bile at levels that are 15 times higher than the simultaneous plasma levels. |
| Irinotecan liposome (Onivyde) | Pancreatic adenocarcinoma | In combination with fluorouracil and leucovorin after disease progression following gemcitabine-based therapy | Diarrhea | The metabolism of irinotecan liposome has not been evaluated. Irinotecan is metabolized as above. | The elimination of irinotecan liposome has not been evaluated. Irinotecan is eliminated as above. |

dose-limiting toxicity of topotecan is myelosuppression with potentially severe neutropenia and thrombocytopenia occurring in approximately 80% and 30% of patients, respectively.

**TOP1 Inhibitors in Clinical Development**

With the goal of mitigating the shortcomings of camptothecins and their derivatives, several camptothecin analogues derived from modifications to the parent drug are in clinical development. Belotecan hydrochloride is a water-soluble camptothecin analogue and gimatecan is a lipophilic oral camptothecin analogue. However, clinical results do not indicate a substantial benefit of these agents compared with approved camptothecin analogues.

The NCI in collaboration with Purdue University (West Lafayette, IN) developed the indenoisoquinolines to overcome the limitations of camptothecins (ref. 4; Supplementary Table S1) including chemical instability, lability of the TOP1CCs that reverse within minutes upon camptothecin withdrawal (37), high arterial flux by the ABCG2 (MRP) and ABCB1 (P-glycoprotein) ABC transporters (38, 39), short plasma half-life, and severe diarrhea. Three indenoisoquinolines are in clinical development (Fig. 1A, left): LMP400 (indotecan), LMP776 (indimitecan), and LMP744 (40, 41).

**TOP1 Inhibitors as Payloads for Tumor-Targeted Delivery**

A growing array of tumor-targeted drug delivery strategies are in clinical development including liposomal or nanoparticle formulations and coupling to mAbs (Table 2). Encapsulating camptothecins in a protective environment until they are released in the tumor can overcome the chemical inactivation of camptothecin lactone in the serum, their rapid blood clearance and dose-limiting bone marrow toxicity. Compared with more toxic payloads (such as the highly toxic DNA cross-linking agents or microtubule poisons), the camptothecins allow sufficient tumor delivery while keeping normal tissue toxicity manageable.

**Camptothecin derivatives for liposome and nanoparticle delivery**

Liposomes and nanoparticles (polymeric micelles, polymeric nanoparticles, and liposomes) provide a physical approach to targeted delivery by preferential accumulation in the tumor owing to pressure created by limited lymphatic drainage and increased permeability of blood vessels—a process termed enhanced permeability and retention (EPR; Table 2). In addition, these formulations protect the drug from degradation, reduce renal clearance, and potentially allow sustained release in the tumor.

Nanoliposomal irinotecan (MM-398, Onivyde) was approved for pancreatic cancers in 2015 (42). The liposome is designed to keep irinotecan in circulation while increasing and prolonging intratumoral drug levels. Compared with free irinotecan, MM-398 exhibits lower Cmax, longer half-life, higher AUC, smaller volume of distribution, and slower plasma clearance for the released SN-38 (43). In preclinical models, MM-398 administered at doses 5-fold lower than irinotecan achieved similar intratumoral exposure with better antitumor activity (42). Despite the pharmacokinetic benefits and delivery advantage, diarrhea occurs frequently and is severe or life-threatening in 20% of the cases (44). This is
likely related to the hepatic accumulation of liposomes and biliary release of SN-38-glucuronide.

Although the EPR improves tumoral delivery of nanoparticles, it has been reported to be <2-fold compared with normal organs (45), and the extent and variability of EPR in tumors is not well-established (46). Nanoparticle delivery efficiency is also influenced by a number of barriers including the mononuclear phagocytic system of the liver, spleen, and other organs, which identify nanoparticles as foreign substances that need to be sequestered, degraded, and eliminated, as well as renal clearance that competes with tumor delivery (47). In animals, the nanoparticle delivery efficiency, that is, the percentage of the injected dose of nanoparticles that reach the tumor is <1% (47). Strategies to improve drug delivery profiles include the use of ligands or targeting moieties to drive nanoparticles to tumors.

**Camptothecin derivatives as warhead for antibody–drug conjugates**

Antibody–drug conjugates (ADC) use mAbs to target tumor cells expressing specific surface antigens to deliver cytotoxic payloads (48). The four FDA-approved ADCs and most others in development use highly cytotoxic payloads targeting tubulin or cross-linking DNA. Camptothecins being less toxic payloads (see above) are increasingly used to enhance both the therapeutic index and tumor delivery (49). Saituzumab govitecan (IMMU-132) and trastuzumab deruxtecan (DS-8201) are the two most advanced camptothecin-based ADCs (Table 2) with promising activity.

**Table 2. Camptothecins as warheads for targeted delivery**

| Name                     | Active derivative (payload) | Formulation (target) | Company                |
|--------------------------|----------------------------|----------------------|------------------------|
| NLG207 (CRLX101)         | Camptothecin               | Liposome             | Ipsen                  |
| NKTR-102                 | Etilirinotecan             | PEG                  | Nektar                 |
| PLX3038                  | SN-38                      | PEG                  | ProLynx                |
| Saituzumab govitecan (IMMU-132) | SN-38              | ADC (TROP2)           | Immunomedics            |
| Labeluzumab govitecan (IMMU-130) | SN-38              | ADC (CEACAMS)         | Immunomedics            |
| IMMU-140                 | SN-38                      | ADC (HLA-DR)         | Immunomedics            |
| Trastuzumab deruxtecan (DS-8201) | DXd               | ADC (HER2)            | Daiichi Sankyo         |
| Patritumab deruxtecan (US-1402) | DXd               | ADC (HER3)            | Daiichi Sankyo         |
| DS-1062                  | DXd                        | ADC (TROP2)           | Daiichi Sankyo         |
| PEN-866                  | SN-38                      | Hsp90-drug conjugate | Tarveda                |
| NK012                    | SN-38                      | PEG-polyglutamate     | Nippon Kayaku          |

IMMU-132 delivered 20–136-times more SN-38 to tumors than irinotecan with tumor-to-serum AUC ratio 20–40-times higher than with irinotecan (52). Antitumor activity has been observed in patients with platinum-resistant urothelial carcinoma, non–small cell lung cancers, and small-cell lung cancers (SCLC; refs. 53, 54).

DS-8201 consists of camptothecin derivative denuxtecan mesylate (DX-8951I) coupled to a humanized anti-HER2 antibody by an enzymatically cleavable peptide linker with a drug to antibody ratio of 8 (55). In preclinical studies, DS-8201 was effective even in tumors with low HER2 expression and tumors that were resistant to ado-trastuzumab-emtansine (T-DM1), a tubulin inhibitor–based ADC. In a phase I study, no dose-limiting toxicities were observed and the MTD was not reached (56). Consistent with preclinical observations, tumor responses were seen in patients with prior T-DM1 and in low HER2-expressing tumors. DS-8201 is being evaluated in patients with HER2-positive, unresectable, and/or metastatic breast cancer who are resistant or refractory to T-DM1.

Both IMMU-132 and DS-8201 have received FDA breakthrough designations for TNBC and HER2 positive (Table 2). The durable responses suggest that camptothecin payloads have a higher tolerability allowing for higher doses than the more toxic FDA-approved ADCs. The lower frequency of severe adverse events compared with irinotecan in both the ADCs could be attributed to the delivery of the camptothecins in their active, non-glucuronidated form, as IgG-bound SN-38 is protected from glucuronidation (50, 52).

Additional camptothecin-derived ADC are being developed against HER3 (ERBB3), TROP2 (TACSTD2) and carcinoembryonic antigen (CEA) (Table 2).

**Combinations of TOP1 Inhibitors with DNA Damage Response Inhibitors and Approaches for Combinations**

Combinations with PARP inhibitors are highly effective in cell line and tumor models with and without HRD (24, 57–59). Preclinical data show PARP catalytic inhibition rather than PARP trapping is sufficient for this synergy (24). Despite promising preclinical data, PARP inhibitor combinations have proven challenging in clinic (Table 3). Dose-limiting myelosuppression has severely limited the ability to dose escalate both PARP inhibitor and chemotherapy in several clinical studies (40, 60–65). For example, the PARP inhibitor, veliparib, in combination with topotecan was found highly
myelosuppressive, requiring dose reductions for both agents (40) with the MTD of veliparib and topotecan only 3% and 40% of the respective single-agent MTDs.

With the growing availability of potent and specific DNA damage response (DDR) inhibitors (such as ATM, ATR, WEE1, DNA-PK, and others), pharmacologic inhibition of DDR in patients is an area of intense study. Strategies to enhance antitumor efficacy with DDR inhibitor–TOP1 inhibitor combinations while mitigating the unacceptable normal tissue toxicities are imperative. One approach involves an innovative “gapped-schedule” that incorporates tumor-targeted DNA-damaging chemotherapy delivery and dose scheduling of DDR inhibitors, that is, sequential intermittent dosing as opposed to continuous dosing. In this approach (Fig. 2), the tumor-targeted TOP1 inhibitor is administered first, followed after a 2–3-day gap by the DDR inhibitor. The gapped-schedule ensures that when the DDR inhibitor is introduced, the tumor remains loaded while normal tissue including bone marrow is cleared of the TOP1 inhibitor (Fig. 2). Supporting this concept is preclinical data showing differential effects on DNA damage in tumor versus the bone marrow using targeted DNA-damaging chemotherapy and two ongoing trials to test this concept in clinic (ClinicalTrials.gov Identifier: NCT02769962 and NCT02631733).

### Combinations with Immunotherapy

Both innate and adaptive immune responses induced by TOP1 inhibitors are emerging as potential mechanisms to increase the antitumor efficacy of immunotherapies. TOP1 inhibitors augment antigen production in melanoma cells (66) and upregulate the expression of MHC class I and IFNβ in breast cancer cells (67). Overexpression of these antigens enhances recognition of tumor cells by T cells and T cell–mediated cytotoxicity (67, 68). Accordingly, greater tumor control was achieved with MM-398 in combination with anti-PD1/-L1 antibodies in immunocompetent mouse melanoma models (68). In a syngeneic TNBC model, topotecan was shown to activate the stimulator of interferon genes (STING)-controlled innate immune pathway and CD8+ T-cell activation. Notably, the antitumor effects were decreased in mice lacking STING (69).

Tumor-targeted delivery of TOP1 inhibitors may represent an opportunity to capitalize the favorable immunomodulatory effects of TOP1 inhibitors, increased genomic DNA damage, antigen presentation, and inflammatory responses, with less toxicity. A recent study showed that DS-8201 is particularly effective in eliciting antitumor immunity in immunocompetent mouse models with human HER2+ expressing cancer cells (70).

### Table 3. Dose levels of TOP1 and PARP inhibitors achieved in combination in clinical trials

| Combination | MTD | TOP1 % of MTD | PARP % of MTD | DLT |
|-------------|-----|---------------|---------------|-----|
| Irinotecan Olaparib | Irinotecan 200 mg/m²; q5w olaparib 50 mg qd d1–21 | 57% | 6% | Diarrhea, myelosuppression |
| Irinotecan Veliparib | Irinotecan 125 mg/m² q2w; olaparib 50 mg bid d1–5 | 69% | 12% | Anorexia/fatigue |
| Topotecan Olaparib | Topotecan 1 mg/m²/d; q3w olaparib 100 mg bid d1–21 | 80% | 10% | Diarrhea, fatigue, myelosuppression |
| Topotecan Veliparib | Topotecan 0.6 mg/m²/d; q2w veliparib 10 bid d1–5 | 40% | 3% | Myelosuppression |
| Topotecan Veliparib | Topotecan 3 mg/m² d2, 9, 16; q4w veliparib 300 mg bid d1–3, 8–10, 15–17 | 75% | 75% | Myelosuppression |

Abbreviations: DLT, Dose-limiting toxicity; PARPi, PARP inhibitors; TOPPi, TOP1 inhibitors.

**Figure 2.** Rationale for gap-scheduling combination therapies with tumor-targeted TOP1 inhibitors (TTTi) and DNA damage response inhibitors (DDRi; such as PARPi, ATRi or ATMi etc). The TTTi given on day 1 of each cycle initially produces TOP1cc both in normal and tumor tissues (brown area). After a 2–3 day gap, the TTTi is selectively retained in tumor tissues (green area). Treatment with the DDRi is then initiated (red arrows) while TOP1cc are present in the tumor tissues but not in normal tissues. The DDRi is stopped 1–2 days before the next cycle. Such “gap-schedule” avoids overlapping toxicity for normal tissues.
This effect was primarily dependent on the payload, in this case a camptothecin derivative, delivered into HER2-expressing tumors by the ADC. The antitumor effect was accompanied by increased expression of MIC class I in tumor cells, increased expression of dendritic cell activation markers, and increase of tumor infiltrating CD8\(^+\) T cells (70).

Conclusions and Future Directions

TOP1 inhibitors are targeted therapies. Like PARP inhibitors, they are synthetic lethal with HRD. Understanding and overcoming the limitations of camptothecins has led to the development of the indenoisoquinolines. Precision therapeutics with TOP1 inhibitors may be achieved by converging approaches: (i) implementing molecular determinants of tumor response, including expression of TOP1 and TDPI, BRCAness and HR, as well as SLFN11; (ii) targeted delivery with tumor-specific antibodies; (iii) improving the warhead such as in the case of the indenoisoqui- nolines; and (iv) rational and tolerable combination therapies based on mechanistic molecular preclinical models and novel drug delivery schedules.

Disclosure of Potential Conflicts of Interest

Y. Pommier is an inventor of NIH patents LMP400, LMP744, and LMP776. A. Thomas and Y. Pommier report grants from AstraZeneca, Tarveda, Newlink, and Gibson to the National Cancer Institute (CRADA) for conduct of basic and clinical research studies. No other potential conflicts of interest were disclosed.

Acknowledgments

The work of both the authors is supported by the NCI Intramural Program, Center for Cancer Research (Z01 BC006 150 and ZIA BC 011793).

Received April 2, 2019; revised May 6, 2019; accepted June 17, 2019; published first June 21, 2019.

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