DNA Topoisomerase I-Targeting Drugs as Radiation Sensitizers

By Allan Y. Chen, MD, PhD [2], Hak Choy, MD [3], and Mace L. Rothenberg, MD [4]

Combination chemoradiation, alone or as an adjuvant to surgery, has been shown to improve treatment outcomes in a number of human malignancies, but may be limited by normal tissue toxicities. A primary challenge in...
broad spectrum antitumor activity in animal models, especially against colon tumors, led to clinical trials in the early 1970s. However, trials were terminated due to observations of excessive toxicity with the ring-open form of camptothecin (camptothecin, sodium salt, NSC-100880). It is now clear that the ring-open form of camptothecin is inactive against its molecular target, topoisomerase I.[24] Among camptothecin derivatives, topotecan is positively charged and irinotecan (CPT-11[Camptosar]) is a prodrug that generates its active metabolite SN-38 intracellularly via carboxyl esteration. Both topotecan and irinotecan demonstrated efficacy in clinical trials,[24,25] and in 1997 were approved by the US Food and Drug Administration (FDA) for the treatment of recurrent colon cancer and ovarian cancer, respectively. S-phase-specific cytotoxicity,[12,13,15] selective cytotoxicity against tumorigenic over nontumorigenic cells,[26,27] and the ability to overcome MDR1-mediated drug resistance,[28,29] are features of camptothecin derivatives that may contribute to their excellent anticancer activity.

Fork Collision Model

Our current understanding of the cytotoxic mechanism of camptothecin is demonstrated by the fork collision model (Figure 3), which was proposed based on studies both in cultured cells and in cell-free extracts.[5] Upon binding of topoisomerase I to DNA, two different reaction intermediates, the noncleavable complex and the cleavable complex, are formed. In a relaxation reaction in the absence of drugs, the cleavable complex and the noncleavable complex are at equilibrium. By inhibiting the rejoining step, topoisomerase I drugs perturb this equilibrium by trapping a reversible topoisomerase I-camptothecin-DNA ternary reaction intermediate, the topoisomerase I cleavable complex. The perturbed equilibrium can be rapidly reversed by removing drug molecules from the medium. Studies using cell synchronization techniques and specific inhibitors of DNA polymerases indicate the involvement of active DNA synthesis in the induction of the highly S-phase-specific camptothecin cytotoxicity.[30,31] It is currently hypothesized that the collision between the replication machinery and the drug-trapped topoisomerase I cleavable complex leads to eventual G2-phase cell-cycle arrest and cell death. A similar cytotoxic mechanism has been proposed for some newly identified topoisomerase I-targeting drugs, including the MGBLs Hoechst 33342 and Hoechst 33258.

Radiosensitization Mechanism of Topoisomerase I-Targeting Drugs

Understanding the mechanism of interaction between topoisomerase I-targeting drugs and ionizing radiation is a prerequisite toward successful use of their combination in cancer treatment. Controversial early studies using cultured cells and human xenografts suggested that camptothecin derivatives modulate the cytotoxic effects of ionizing radiation.[32-39] To answer key questions, such as whether camptothecin derivatives are radiosensitizers and whether DNA topoisomerase I is involved in such radiosensitization, we conducted clonogenic survival assays using cultured mammalian cells.[40] We found that drug incubation with camptothecin derivatives radiosensitized log-phased human MCF-7 breast cancer cells in a schedule-dependent manner (Table 1).[40] The radiosensitization effect was observed when the cells were exposed to drug treatment before or concurrent with radiation treatment, but not after radiation treatment (Table 1). The implication based on this observation is that camptothecin derivatives should be administered before or concurrently with radiation during chemoradiation clinical trials to optimize the radiosensitization effect.

Stereo-Specific Interaction

Camptothecin derivatives interact with DNA topoisomerase I in a stereo-specific fashion.[30] For example, assayed by the ability to induce topoisomerase I-mediated DNA cleavage, the 20(S)-stereoisomer of 10,11-methylenedioxyacamptothecin is 10,000-fold more active than its 20(R)-isomer (see Figure 4A). This pair of camptothecin derivatives was used to investigate the role of DNA topoisomerase I in mediating radiosensitization. As shown in Figure 4B, only the 20(S)-10,11-methylenedioxyacamptothecin radiosensitized human breast cancer MCF-7 cells. The prerequisite role of such an intact stereo-specific interaction in the induction of radiosensitization was further supported by the observation that the mutant topoisomerase I-containing DC3F cells were relatively resistant to radiosensitization.[40-42]

DNA Repair Inhibition

Some investigators have suggested DNA repair inhibition as a mechanism of radiosensitization by camptothecin derivatives.[37] If this theory is correct, a larger radiosensitizing effect should be observed in cells that are growth inhibited (G0/G1 cells) to maximize their repair function for...
potentially lethal damages.[37] We found that camptothecin only minimally enhanced the cytotoxic effect of radiation in plateau phase cells, which were arrested by growing to confluency, as well as in synchronized G1-phase cells obtained by mitotic shake-off technique.[40] This finding may indicate a possible therapeutic advantage of camptothecin derivatives to radiosensitize actively proliferating cancer cells selectively.

The molecular mechanism of radiosensitization of DNA topoisomerase I-targeting drugs remains to be defined. Based on available information, a plausible mechanism of radiosensitization of topoisomerase I drugs is proposed (Figure 5). It is possible that induction of radiosensitization is originally initiated by the topoisomerase I-trapped cleavable complex. This drug-stabilized cleavable complex, with a concealed single-strand DNA break, may be viewed as a [potentially sublethal] DNA damage. Interaction with as yet undefined cellular processes such as DNA replication, RNA transcription, and DNA repair may transform such [potentially sublethal] DNA damage into [sublethal] DNA damage. It is plausible that such [sublethal] DNA damage could then be converted into [lethal] DNA damage with the addition of radiation-induced DNA damage.

Clinical Chemoradiation Trials of Camptothecin Derivatives

All of the topoisomerase I-targeting drugs currently in clinical development are camptothecin derivatives. Among them, irinotecan, topotecan, and 9-aminocamptothecin are the most extensively studied.[25,26] A wide spectrum of clinical antitumor activity, including activity against gastrointestinal tract cancer, ovarian cancer, small-cell lung cancer, non-small-cell lung cancer, and malignant lymphomas has been observed with camptothecin derivatives.[25,26] Based on clinical success as systemic therapy, chemoradiation trials of irinotecan and topotecan for a variety of solid tumors are currently ongoing.

Phase I/II Trials

Table 2 shows some clinical phase I/II chemoradiation trials of irinotecan (CPT-11) for patients with locally advanced non-small-cell lung cancer.[43-46] In general, impressive objective response rates ranging from 60% to 80% have been achieved in patients treated with various chemoradiation combinations with irinotecan and carboplatin. The incidence of grade 3 or greater treatment-related toxicities (ie, fever, neutropenia, thrombocytopenia, pneumonitis, and esophagitis) was low (Table 2). The regimen of concurrent radiation with weekly carboplatin and irinotecan will most likely be adopted by the Radiation Therapy Oncology Group (RTOG) as one treatment arm in a new randomized phase II trial in patients with locally advanced non-small-cell lung cancer. The efficacy of irinotecan, either used as second-line treatment for 5-FU-refractory tumors or as first-line treatment for colorectal cancer, has also been well established by clinical trials.[47] Clinical trials using combination therapy with irinotecan and radiation for locally advanced colorectal cancer appear to be the next logical step in improving treatment outcomes in this group of patients.

The clinical use of topotecan in the chemoradiation setting is currently being explored in non-small-cell lung cancer and tumors of the central nervous system. A combination of cranial irradiation and topotecan is being evaluated by the RTOG and the Children’s Cancer Group (CCG) in patients with glioblastoma and pontine gliomas, respectively.

Conclusions and Future Directions

In conclusion, an intact stereo-specific interaction between drug molecule and topoisomerase I is a prerequisite step for the induction of DNA topoisomerase I-mediated, schedule-dependent radiosensitization in mammalian cells. Future studies are needed to increase our understanding of the mechanisms underlying radiosensitization by camptothecin derivatives. As yet unresolved issues include mechanisms of schedule dependence, the role of cell-cycle distribution, the influence of hypoxia, as well as the role of DNA replication and repair. It will also be interesting to test the potential radiosensitizing effects of other new topoisomerase I-targeting drugs such as the DNA MGBLs.[5,40]

An understanding of the molecular radiosensitization mechanism induced by topoisomerase I-targeting antitumor drugs may also facilitate the development of more effective radiosensitizers for cancer treatment. Only when the detailed mechanisms of interaction between drugs and radiation have been established can efficacious, novel chemoradiation regimens be accurately designed and tailored against different kinds of cancer. Chemoradiation using topoisomerase I-targeting drugs is currently being investigated and may prove to be an effective therapy against several kinds of human solid tumors. Recent advances in the field of DNA topoisomerase I provide a unique opportunity to translate basic science research into improvements in cancer treatment.
References:


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