REVIEW ARTICLE

DNA topoisomerase I drugs and radiotherapy for lung cancer

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ABSTRACT

Lung cancer represents the most common cause of cancer-related mortality in the United States and around the world. DNA topoisomerase I (TOP1) drugs such as irinotecan and topotecan represent a unique class of chemotherapeutic agents that exhibit not only potent cytotoxic effect, but also tumor-selective radiation-sensitizing effect. The mechanism of cytotoxicity and radiation sensitization by TOP1 drugs has been intensely investigated. Modern radiotherapy, aided by improved imaging and treatment delivery technology, is capable of targeting tumors more precisely, while sparing surrounding critical structures. Clinical trials with camptothecin derivatives and radiotherapy have been conducted in lung cancers. Combined modality therapy with TOP1 drugs and radiotherapy offers a new frontier for lung cancer therapy. We review the present state of TOP1-targeted chemotherapy and modern radiotherapy for lung cancer.

KEY WORDS

DNA topoisomerase I (TOP1); camptothecin derivative; radiation therapy; lung cancer; radiation sensitizer

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Introduction

In 2012, more than 1.6 million new cancer cases and close to 0.6 million deaths (about 35% of new cases) from cancer are projected to occur in the United States (1). Albeit small improvement, it has been noted that the overall cancer death rates from 2004 to 2008 have decreased by 1.8% per year in men and by 1.6% per year in women (1). Lung cancer represents the most common cause of cancer-related mortality in the United States and around the world. Despite medical advances, lung cancer still accounts for more than 150,000 deaths annually in the United States (1).

While surgical intervention with lobectomy and mediastinal lymph node dissection is considered the standard of treatment for early-stage non-small cell lung cancer (NSCLC) (2), systemic chemotherapy and local field radiotherapy are the mainstay therapies for small cell lung cancer (SCLC) and advanced-stage NSCLC (3,4). Radiotherapy plays important roles in both curative and palliative treatment for lung cancer patients (5). An estimated 76% of lung cancer patients might benefit from radiotherapy (6). Guided by much improved imaging modalities, new radiotherapy technologies make possible the delivery of highly conformal radiation to the tumor target with precision (7,8). However, given the similar radiation sensitivities shared by most solid tumors and their counterpart normal tissues and the fact that radiation beams inevitably irradiating through tissues surrounding the target, the efficacy of radiotherapy remains largely constrained by the potential radiation-induced toxicities upon the normal tissues (9,10).

Combining chemotherapy with radiotherapy represents a key oncology strategy for a more comprehensive attack toward cancers. Combination chemoradiotherapy has been shown to improve treatment outcome for various solid tumor malignancies including lung cancer. By treating overt or microscopic metastatic lesions, systemic chemotherapy complements local primary tumor control provided by radiotherapy. In addition, a number of chemotherapeutic drugs exhibit radiation-sensitizing activity and are capable of enhancing efficacy of radiotherapy targeting at primary tumor (10,11). DNA topoisomerase I (TOP1)-targeted camptothecin derivatives represent a novel class of anticancer agents that exhibit potent cytotoxicity (12-14), as well as tumor-selective radiation-sensitizing effect toward a variety of solid tumors (14-16). Combination therapy with TOP1 drugs and radiotherapy has great potential to improve treatment efficacy and decrease normal tissue toxicities. Enhancement of radiotherapy with TOP1 drugs offers a new frontier for cancer therapy. In this article, we review the present state of TOP1-

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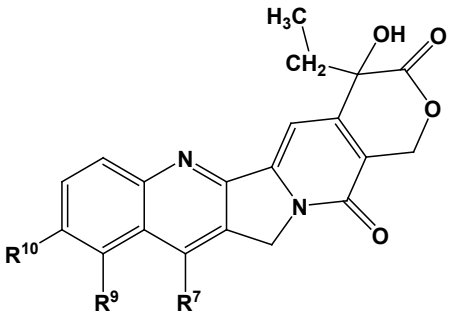


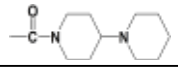
Name	R^7	R^9	R^{10}
camptothecin	H	H	H
Topotecan	H	(CH_2)-$N^+(CH_3)_2H$	OH
Irinotecan	H	H	

Figure 1. Chemical structures of camptothecin, topotecan and irinotecan.

targeted chemotherapy and modern radiotherapy from basic science to clinical applications in lung cancers.

DNA topoisomerase I as a therapeutic target

DNA topoisomerases I (TOP1) and II (TOP2) are essential nuclear enzymes that catalyze the interchange of DNA double-helix between various topological states. Human TOP1 is involved in RNA transcription, DNA replication and maintaining genome stability by regulating the supercoiling state of DNA (reviewed in 17). The cellular level of TOP1 is up-regulated in both slow and rapidly proliferating tumor cells (18,19). This provides a scientific basis for tumor-selective targeting by TOP1 drugs.

A number of anticancer compounds, including camptothecins (13), DNA minor groove-binders (20) and indolocarbazole derivatives (21,22), have been demonstrated to exert their cytotoxic effect through TOP1. Camptothecin and its derivatives (Figure 1) are the currently best-characterized TOP1-targeting anticancer drugs. Topotecan (Hycamtin) and irinotecan (Camptosar, CPT-11) were initially approved by the FDA for treatment of recurrent ovarian and colon cancers, respectively (23). Based on their demonstrated efficacies in clinical trials, the clinical usage of topotecan and irinotecan has been rapidly expanded to include other cancers such as NSCLC and SCLC (24).

DNA topoisomerase I drugs as radiation sensitizers

DNA is the critical molecular target for ionizing radiation (25), with double-strand DNA break being the major type of lethal lesion (26). Generally, radiation sensitizers may enhance radiation cytotoxicity by means of increasing amount of DNA damage, inhibiting repair of DNA damage or re-distributing cells into radiation-sensitive phases of the cell cycle, such as the G2/M and G1 phases (27). In addition to diverse mechanisms of action, factors affecting bioavailability at the target site are major determinants for the effectiveness of different radiation sensitizers.

Recent advances in studying the radiation-sensitizing effect of TOP1 drugs in preclinical systems have contributed greatly to the clinical application of combined modality therapy with radiation and TOP1-targeted drugs (14). For example, camptothecin derivatives were shown to induce radiation sensitization in cultured human breast cancer MCF-7 cells in a schedule-dependent manner that requires drug treatment prior to, but not following radiation (15). This observation indicates the importance of treating patients with TOP1 drugs prior to delivery of radiotherapy. Based on studies using DNA polymerase inhibitors and phase-specific cells sorted by cell-cycle sorting techniques, the induction of TOP1-mediated radiation sensitization in mammalian cells was shown to be an S-phase-specific event that requires active DNA synthesis (28). This finding indicates a probable therapeutic advantage of TOP1 drugs in selectively radiosensitizing proliferating cancer cells that are actively synthesizing DNA.

Eukaryotic cells have evolved two major repair pathways for DNA double-strand breaks (DSB) including the homologous recombination and the non-homologous end-joining (NHEJ) pathways (29). Inactivation of the NHEJ pathway was demonstrated to significantly enhance TOP1-mediated radiation sensitization, but not cytotoxicity, in preclinical cultured mammalian cells (28). This study suggests TOP1 drugs may induce a unique NHEJ-dependent radiation sensitization pathway that is distinctive from their cytotoxicity pathway (Figure 2). It is

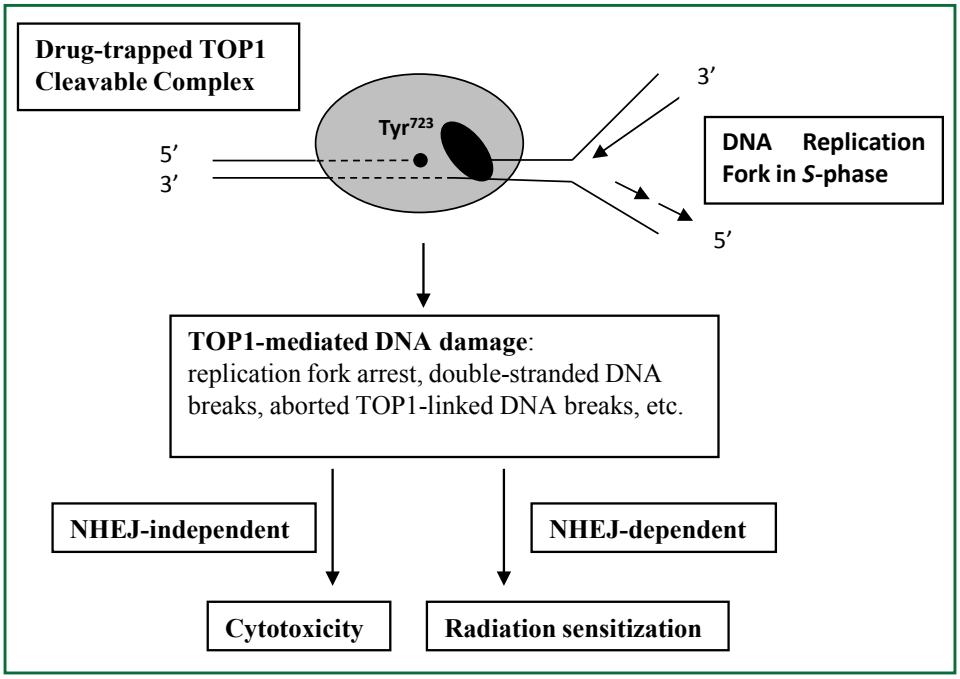


Figure 2. A model for TOP1-mediated cytotoxicity and radiation sensitization. In this model, the drug-trapped TOP1 cleavable complex initiates TOP1-mediated DNA damage by "interacting" with replication fork during DNA synthesis. Double strand DNA breaks, replication fork arrest and an aborted "cleaved" TOP1-DNA complex can be generated. Based on the dependence on NHEJ double-strand DNA repair, current data indicate dissociation between the pathways lead to TOP1-mediated cytotoxicity and TOP1-mediated radiation.

conceivable that inhibitors of NHEJ pathway can be used clinically to enhance radiosensitizing effect of TOP1 drugs.

Modern precision radiotherapy in early stage non-small cell lung cancer

With the innovations of stereotactic radiosurgery, three dimensional (3-D) radiation treatment planning, IMRT (intensive modulated radiation therapy), VMAT (volumetric modulated arc therapy) and image-guided radiation therapy (IGRT), radiotherapy has experienced an unprecedented technical advancement in the recent 20 years (7,8). Four-dimensional CT (4D-CT) represents a major breakthrough that allows accurate determination of internal target volume (ITV) for mobile lung tumors in individual patients (30,31).

Conceptually derived from cranial stereotactic radiosurgery, stereotactic body radiation therapy (SBRT) has been emerging as an excellent alternative for medically inoperable early stage NSCLC patients. In lung SBRT, a total of 45-50 Gy of hypo-fractionated radiotherapy is delivered in 3-5 fractions over a 10-20 days' duration. Available data have shown an impressive 80-95% local tumor control at 2-5 years and good lung function preservation (8,32). The recently published RTOG 0236 phase II study demonstrated 3-years 98% local tumor control and 56% survival (7). These results are comparable to the 5-year 53% survival with surgical resection, based on a compiled result from thousands of patients in the International Association for the Study of Lung Cancer Staging Project (8). Though with demonstrated impressive effectiveness, the usage of any newly developed medical technology such as SBRT requires special caution. A recent report of fatal central-airway necrosis in a patient with a centrally-located lesion treated with SBRT highlights the importance of long-term follow-up for SBRT-treated patients (33).

Modeling exercises demonstrate that significant increases in biologically equivalent dose may be achieved with the addition of radiation sensitizers to hypo-fractionated radiotherapy (34). How to incorporate the cytotoxic and radiosensitizing effects of TOP1 drugs with modern precision hypo-fractionated radiotherapy for lung cancer remains to be explored.

Clinical trials of camptothecin derivatives and radiotherapy in lung cancer

A large number of clinical trials have demonstrated efficacy of TOP1-targeted camptothecin derivatives in the treatment of NSCLC, as well as SCLC.

Clinical chemotherapy trials of camptothecin derivatives in SCLC and NSCLC

Topotecan is currently a standard second-line therapy for patients with SCLC (35,36). Single agent regimen with daily intravenous infusion of 1.5 mg/m^2 in 30 min for first 5 days of a 21-days cycle demonstrated comparable outcomes as a three-drug combination with cyclophosphamide, doxorubicin and vincristine for recurrent SCLC patients (37). Topotecan is FDA approved for patients with SCLC who relapse after first line chemotherapy (4).

Combination irinotecan and cisplatin has been shown to improve survival than the standard regimen of etoposide and cisplatin for extensive-stage SCLC in a Japan Clinical Oncology Group (JCOG) phase III study (38). Interestingly, a subsequent larger North American SWOG S0124 trial only demonstrated statistically comparable efficacies for both regimens (39). Irinotecan-containing regimens were noted to cause less severe hematological side effects in neutropenia and thrombocytopenia, but more severe gastroenterological toxicities in vomiting and diarrhea than the etoposide and cisplatin regimen. Noteworthy mentioning, a laboratory correlated pharmacogenomics analysis of the SWOG S0124 trial indicated that ABCB1 (C3435T) T/T (membrane transport) and UGT1A1 (G-3156A) A/A (drug metabolism) genotypes are related to the irinotecan-related diarrhea and neutropenia, respectively. In a recent meta-analysis of six trials involving about 1,500 chemo-naïve extensive-stage SCLC patients, irinotecan and platinum combination regimens did demonstrate greater overall survival than etoposide and cisplatin combination (40).

Studies showed that irinotecan is an active chemotherapeutic agent for metastatic NSCLC with acceptable toxicities. As a single agent or in combination with cisplatin, irinotecan has demonstrated promising efficacy with up to 30% response rate and a median survival of 50 weeks in previously untreated NSCLC patients (41,42).

Clinical chemoradiation trials of camptothecin derivatives in NSCLC

Many clinical studies have demonstrated the feasibility and efficacy of TOP1 drugs in combination with thoracic radiotherapy for locally advanced NSCLC (Table 1).

Weekly injection of irinotecan with concurrent thoracic radiotherapy for locally advanced NSCLC has been studied in a number of phase I and II trials. In these studies, MTD of intravenous injection of irinotecan, administered weekly for 6 weeks concurrently with thoracic radiotherapy to 60 Gy, was shown to be from 40 to 60 mg/m^2 (43-46). Dose-limiting toxicities included esophagitis, pneumonitis, diarrhea, nausea and vomiting. A generally good response rate of 58% to 79% was reported (43-46).

Irinotecan, in combination with cisplatin-based chemotherapy and daily thoracic radiotherapy, has also been tested in stage III NSCLC patients. A phase I/II trial with irinotecan and cisplatin chemotherapy (4-weeks interval, a total of 3 cycles), and 60 Gy of thoracic radiotherapy was conducted by Yokoyama *et al.* (48). Leukopenia and diarrhea were the dose-limiting toxicities, and an overall response rate of 67% was reported. In another phase I/II trial with 30 patients with unresectable stage III NSCLC, weekly irinotecan and daily carboplatin (20 mg/m^2/day, 5 days weekly for 4 weeks) were administered with concurrent 60 Gy of thoracic radiotherapy (49). The MTD of irinotecan was determined to be 60 mg/m^2, with pneumonitis, nausea and vomiting as dose-limiting toxicities. An objective response rate of 60% was observed in the study.

Single agent topotecan, given by daily bolus injection on days 1 to 5, and days 22 to 26, was dose-escalated with concurrent daily thoracic radiotherapy in a Phase I study for 12 patients with unresectable locally advanced NSCLC (50). Dose-limiting toxicities included esophagitis and neutropenia, and the MTD was 0.5 mg/m^2/day. A response rate of 17% with 2 complete responses was reported. Another phase I study was conducted with escalating both thoracic radiotherapy and infusion duration of topotecan at constant dose 0.4 mg/m^2/day. The radiation dose (30, 40 and 60 Gy) and topotecan infusion duration (21, 28, 35 and 42 days) were escalated in an alternating fashion at different dose levels (51). Studies reported well-tolerated side effects and recommended 60 Gy thoracic radiotherapy and 42-day duration of topotecan 0.4 mg/m^2/day as the phase II regimen. A good 43% response rate was reported for a total of 24 patients, including 22 patients with NSCLC.

Clinical chemoradiation trials of camptothecin derivatives in SCLC

A number of clinical phase I/II studies with camptothecins, in combination with cisplatin-based chemotherapy and concomitant thoracic radiotherapy, have shown promising efficacy for SCLC (Table 2). Oka *et al.* conducted a phase I study of irinotecan and cisplatin with concurrent split-course radiotherapy in limited-stage SCLC (52). Patients were treated with four cycles of irinotecan (days 1, 8 and 15) and cisplatin (day 1) at 28-days intervals, together with a total of 60 Gy thoracic radiotherapy commenced on day 2 of each chemotherapy cycle, with 20 Gy in 10 daily fractions administered in the first, second and third cycles of chemotherapy. The MTDs of irinotecan and Cisplatin were determined to be at 50 and 60 mg/m^2, with general fatigue listed as dose-limiting toxicity. An overall response rate of 94% with 4 complete responses was reported for 16 evaluable patients (52).

A paclitaxel/carboplatin/topotecan regimen was evaluated

Table 1. Clinical trials of concurrent TOP1 drugs with thoracic radiotherapy for NSCLC.

Study description	No. of patients	Chemotherapy regimen	Radiation dose	Toxicity	Response rate
Phase II (43)	24	Irinotecan; 60-70 mg/m^2, weekly ×6	60 Gy	Neutropenia esophagitis pneumonitis	79% (19 PR)
Phase I/II (44)	26	Irinotecan; 30-60 mg/m^2, weekly ×6	60 Gy	Esophagitis pneumonitis diarrhea	77% (3 CR, 17 PR)
Phase II (45)	12	Irinotecan; 30-50 mg/m^2, weekly ×6	60 Gy	Nausea/vomiting esophagitis	58% (7 PR)
Phase I/II (46)	26	Irinotecan; 45 mg/m^2, weekly ×6	60 Gy	Diarrhea esophagitis pneumonitis	75% (2 CR, 16 PR)
Phase II (47)	68	Irinotecan + Cisplatin, Induction ×2, then weekly	60 Gy	Neutropenia esophagitis pneumonitis	63% (4 CR, 39 PR)
Phase I/II (48)	12	Irinotecan + Cisplatin, every 4 weeks ×3	60 Gy	Neutropenia diarrhea	67% (8 PR)
Phase I/II (49)	30	Irinotecan weekly, 30-60 mg/m^2, Carboplatin daily for 4 weeks	60 Gy	Neutropenia esophagitis pneumonitis	60% (3 CR, 15 PR)
Phase I/II (50)	12	Topotecan; 0.5-1 mg/m^2, Days 1-5, 22-26	60 Gy	Nausea neutropenia esophagitis	17% (2 CR)
Phase I/II (51)	24	Topotecan; 0.4 mg/m^2, Daily, 21-42 days	30-60 Gy	Neutropenia esophagitis	43% (9 PR, 6 SD)

NSCLC = non-small cell lung cancer; CR = complete response; PR = partial response; SD = stable disease.

Table 2. Clinical trials of concurrent TOP1 drugs with thoracic radiotherapy for SCLC.

Study description	No. of patients	Chemotherapy regimen	Radiation dose	Toxicity	Response
Phase I (52)	17 (all LS)	Irinotecan + cisplatin	60 Gy in 3 split courses of 20 Gy in 10 daily fractions	Fatigue	94% (4 CR, 11 PR)
Phase II (53)	100 (43 LS, 57 ES)	Topotecan + carboplatin +paclitaxel	45 Gy in 25 daily fractions for LD	Neutropenia, thrombocytopenia, fatigue	LS -93% ES -88%
Phase II (54)	78 (all LS)	Topotecan + carboplatin +paclitaxel	61.2 Gy in 34 daily fractions	Neutropenia, thrombocytopenia, fatigue fatal pneumonitis	51% CR SV: 20 months

SCLC = small cell lung cancer; LS = limited-stage; ES = extensive-stage; CR = complete response; SV = median survival.

as the first-line treatment in a phase II study consisting of 43 limited-stage and 57 extensive-stage SCLC patients (53). During the 4 courses of chemotherapy at 21-day intervals (paclitaxel 135 mg/m^2, 1-hour IV infusion, day 1; carboplatin AUC 5.0 IV, day 1; topotecan 0.75 mg/m^2 IV, days 1-3), patients with limited-stage SCLC also received 45 Gy of thoracic radiotherapy in 25 daily fractions, beginning week 6 of chemotherapy. Overall response rate of 90% (extensive-stage 88%; limited-stage 93%) with toxicities including neutropenia, thrombocytopenia and fatigue was reported. In a subsequent study conducted by the same group of researchers, the paclitaxel/carboplatin/topotecan regimen was combined with a higher 61.2 Gy of thoracic radiotherapy to treat 78 patients with limited-stage SCLC (54). A high 51% complete response rate and median survival of 20 months were reported for 68 evaluable patients after a short median follow-up of 12 months. However, in addition to high incidence of neutropenia, thrombocytopenia and fatigue, three treatment-related deaths (2 radiation pneumonitis; 1 pneumonia/neutropenia) were reported (54).

Irinotecan and topotecan chemotherapy in brain metastases from SCLC

Brain metastases occur commonly in SCLC patients. The risk of brain metastases in SCLC patients ranges from 18 to 25% at presentation, to 50% during the 2-year course of disease (55,56). Brain metastases from SCLC are traditionally treated by radiotherapy, since most chemotherapeutic agents exert low efficacies due to factors such as the blood-brain barrier (BBB) that prevents penetration of anticancer drugs into the central nervous system. Nevertheless, recent data suggest that the BBB may be disrupted with the existence of brain metastasis and, consequentially, permeable to anticancer drugs (57).

Irinotecan and topotecan, appear to penetrate the BBB better and exert anticancer activity for brain metastases (58-60). A multicenter phase II study was conducted to evaluate the efficacy of single agent topotecan in 30 patients with SCLC who relapsed with symptomatic brain metastases after previous chemotherapy (30 patients) and whole brain radiotherapy (8 patients). Twenty patients received the initially planned topotecan 1.5 mg/m^2 as a 30-min intravenous infusion for 5 consecutive days every 3 weeks, with the last 8 patients received reduced dose topotecan 1.25 mg/m^2 due to the observed thrombocytopenia (58). An impressive 33% overall response rate, including 3 complete responses and 7 partial responses, and well-tolerated hematological side effects was reported (58). In another phase II trial, 80 patients with metastatic or relapsed SCLC were treated with irinotecan 200 mg/m^2 (chemotherapy naïve patients) or 150 m^2 (previously chemotherapy treated patients), in combination of carboplatin AUC of 5, every 21 days for 6 cycles. An analysis of 14 assessable patients with brain metastases in this study revealed an impressive overall response rate of 65% after 2 cycles of chemotherapy, and a median survival of 6 months (60).

Conclusions

Important information such as the sequence of chemoradiation combination and important determinants for TOP1-mediated radiation sensitization has been obtained through characterization of camptothecin derivatives. Tumor-selective targeting due to the up-regulated level of TOP1 in cancer cells and S-phase specific mechanism may contribute to therapeutic advantages of anticancer chemoradiotherapy with TOP1 drugs. As the understanding of molecular pharmacology progressively influences treatment strategy, a better elucidation of the mechanism of TOP1 drug will lead to development of better chemoradiation regimens.

Clinical trials have demonstrated that irinotecan and topotecan are active anticancer drugs with potent cytotoxicity and radiation sensitization activity for lung cancer. The optimal combination with other chemotherapy drugs, as well as scheduling between TOP1 drugs and thoracic radiotherapy for the treatment of lung cancer remains to be defined. The promising role of irinotecan and topotecan in treating SCLC patients with brain metastases requires further investigation.

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