Topoisomerase I Inhibitors in the Combined-Modality Therapy of Lung Cancer

Review Article [1] | June 01, 2004
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Locally advanced non–small-cell lung cancer represents 30% to 40% of all pulmonary malignancies. Most patients will die of the disease after aggressive contemporary treatments. Therefore, significant improvement in therapeutic methods must be implemented to improve overall survival rates. The arrival of a new generation of chemotherapeutic agents—including the taxanes, gemcitabine (Gemzar), and topoisomerase inhibitors such as irinotecan (Camptosar) and topotecan (Hycamtin)—offers the hope of significant advances in the treatment of lung cancer. Irinotecan and topotecan are camptothecin derivatives that inhibit topoisomerase I enzyme. It is believed that topoisomerase I inhibitors stabilize a DNA/topoisomerase I complex and interact with replication machinery to cause cell death. A significant amount of data demonstrates that these topoisomerase I inhibitors also act as radiosensitizers. With the increasing data that support concurrent chemoradiation treatment for malignancies, including lung cancer and head and neck cancers, there is an impetus to pursue the additional drugs that may potentially improve local control and survival. Irinotecan is undergoing early clinical trials in the combined-modality setting in several different disease sites. This paper will review the data on the role of camptothecin derivatives as a radiosensitizer and as a component of combined-modality therapy for lung cancer. It is hoped that newer treatment strategies, like the combination of radiation and topoisomerase I inhibitors, will have a significant impact on cure rates in the future.

In 2004, it is estimated that in the United States there will be 68,510 deaths among women and 91,930 deaths among men due to lung cancer, which is the leading cause of cancer deaths in the United States. Lung cancer accounts for 14% of new cancer cases and 28% of cancer deaths per year in the United States.[1] The 5-year survival rate for lung cancers has been around 15% from 1974 through 1995.[2] Most of these cures are related to surgical treatment of patients presenting with stage I and II cancers. However, about 35% of patients present with locally advanced disease that is not amenable to surgical therapy but may be potentially curable.[3] Traditional radiation treatment alone in this group of patients has yielded dismal cure rates at 5 years. Therefore, a combined-modality therapy has been sought to improve the poor outcome with single modality alone. Patients with clinical stage IIIA have an overall 5-year survival rate of 10% to 15%. However, this figure drops to 2% to 5% when there is grossly visible disease in the mediastinum on a chest x-ray.[4] The principal forms of treatment for patients with stage III non–small-cell lung cancer (NSCLC) are radiation therapy, chemotherapy, surgery, and combinations of these modalities. Several potential benefits are derived from interactions of radiotherapy and chemotherapy to improve therapeutic outcome. Combined radiotherapy and chemotherapy may increase tumor response, protect normal tissues, and exhibit nonoverlapping toxicities.[5] There is potential synergistic increase in enhancement of tumoricidal effect in specific anatomic sites where single-modality therapy may have limited efficacy. Chemotherapeutic agents may reduce the radiotherapy-induced normal tissue toxicity to an acceptable level for patients. Finally, two partially effective therapeutic modalities may be combined without having to significantly reduce their dose levels to avoid treatment-related toxicities.
Multiple phase III trials have confirmed therapeutic benefits of combining chemotherapy and radiotherapy in locally advanced NSCLC, but with increased treatment-related toxicity.[6-9] A large meta-analysis of 22 trials (3,033 patients and 2,814 deaths) comparing radiotherapy administered alone or with chemotherapy demonstrated a 10% reduction in the relative risk of death with chemoradiotherapy vs radiotherapy as a sole modality ($P = .006$), with an absolute reduction in deaths of 3% at 2 years and 2% at 5 years.[10] Another meta-analysis from Pritchard et al suggested that traditional chemotherapy added to radiotherapy adds an average of 2 months to patient survival.[11] Recent trials have shown that concurrent chemoradiotherapy results in a better overall survival compared with sequential chemoradiotherapy in NSCLC.[12,13] Combined chemotherapy and radiotherapy currently remains the standard treatment for locally advanced NSCLC. However, local failure rates
can be around 80%. Therefore, ongoing trials seek to improve the outcome for treatment of lung cancer. Multiple agents including paclitaxel, docetaxel (Taxotere), vinorelbine, gemcitabine (Gemzar), and irinotecan (Camptosar) show a 20% to 54% response rate for single-agent treatment in metastatic NSCLC. This review will focus on the data surrounding the use of topoisomerase I inhibitors in combination with thoracic radiotherapy in the treatment of locally advanced NSCLC.

Camptothecin

Camptothecin is an alkaloid originally found in the Chinese tree *Camptotheca acuminata*. The US National Cancer Institute first discovered camptothecin with antitumor activity in the 1960s.[14] In preclinical studies, the antitumor activity was seen against colon and gastric cancers and leukemia. However, unpredictable toxicities, including myelosuppression and hemorrhagic cystitis, were seen in patients treated with camptothecin. Greater understanding of the mechanisms of action of camptothecin and development of water-soluble compounds generated greater interest in camptothecin as a potential chemotherapeutic agent. Camptothecin and its derivatives target topoisomerase I, the DNA-relaxing enzyme.[15-18] Although topoisomerase I was discovered in the 1970s, its mechanism of action in DNA replication was not clearly understood until the 1980s. Topoisomerase I was shown to be the target of camptothecin in 1985 by Hsiang et al.[19] This enzyme serves to relax both positively and negatively supercoiled double-helix DNA to allow replication and transcription. It causes reversible single-strand breaks, which allow rotation of the broken DNA strand around the intact strand. The critical step for drug interaction is stabilization of the topoisomerase I/DNA complex that the enzyme forms when cleaving DNA to allow for uncoiling to occur.[15-20] In the presence of camptothecin, a camptothecin/topoisomerase I/DNA complex becomes stabilized because the 5'-phosphoryl terminus of the enzyme-catalyzed DNA single-strand break is bound covalently to a tyrosine residue of topoisomerase I. These complexes are nonlethal and reversible. However, the single-strand breaks become irreversible double-strand breaks when the DNA replication fork collides with reversible complex during S phase or during unscheduled DNA replication. The resulting cell death can be recognized by the p53 damage-sensing pathway and may result in acceleration of apoptosis.[21-24] Thus, the cytotoxic effect of the camptothecin requires active DNA replication. In vitro studies have shown that cells in S phase may be 100 to 1,000 times more sensitive to camptothecin than cells in the G1 or G2 phase of the cell cycle.[25]

### Table 1

**Clinical Trials of Concurrent Irinotecan and Thoracic Radiation Therapy for NSCLC**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Radiation Therapy Dose</th>
<th>Irinotecan Regimen</th>
<th>Acute Toxicity</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kodoh[52]</td>
<td>26</td>
<td>60 Gy</td>
<td>Weekly 45 mg/m² x 6</td>
<td>Esophagitis, Pneumonitis, Diarrhea</td>
<td>8% (2/24) CR, 67% (16/24) PR</td>
</tr>
<tr>
<td>Saka[50]</td>
<td>24</td>
<td>60 Gy</td>
<td>Weekly 60-70 mg/m² x 6</td>
<td>Fever, Neutropenia, Esophagitis, Pneumonitis</td>
<td>79% (19/24) PR</td>
</tr>
<tr>
<td>Takeda[49]</td>
<td>17</td>
<td>60 Gy</td>
<td>Weekly 30-60 mg/m²/wk x 6</td>
<td>Esophagitis, Pneumonitis</td>
<td>13% (2/16) CR, 56% (9/16) PR</td>
</tr>
<tr>
<td>Choy[51]</td>
<td>13</td>
<td>60 Gy</td>
<td>Weekly 30-50 mg/m² x 6</td>
<td>Nausea, Vomiting, Esophagitis</td>
<td>58% (7/12) PR</td>
</tr>
</tbody>
</table>

**CR** = complete response; **NSCLC** = non-small-cell lung cancer; **PR** = partial response.

**Irinotecan** In the 1970s, camptothecin proved to be too toxic as a chemotherapeutic agent. However, one of the water soluble derivatives, irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin) or CPT-11 (Figure 1) displayed antineoplastic activity with improved toxicity profile.[26] Irinotecan was first commercially available in Japan in 1994 for treatment of
lung, cervical, and ovarian cancers. Irinotecan is a prodrug that is metabolized intracellularly to its active metabolite, SN-38, by a carboxyesterase converting enzyme. This metabolite is over 1,000 times more potent as an inhibitor of topoisomerase I than irinotecan.[27,28] All of the camptothecins have a terminal lactone ring, which can be hydrolyzed to a less active form. However, under acidic conditions such as in the microenvironment of a tumor, the active lactone species is favored.[27] The plasma half-life of SN-38 after a short intravenous infusion is approximately 11.5 hours. Thus, a low concentration of the metabolite may remain after 2 days and have cytotoxic effect.[29] The major excretory pathway of SN-38 is via hepatic glucuronidation and a decreased ability to glucuronidate may possibly correlate with increased gastrointestinal side effects. One of the dose-limiting toxicities of irinotecan is delayed onset diarrhea that can be potentially life threatening. The diarrhea is felt to be related to the relatively high S-phase fraction of the intestinal mucosa, as well as to the action of intestinal flora glucuronidase in cleaving the camptothecin glucuronidase conjugate leading to the release of the drug in the intestinal lumen.[30] Other commonly observed toxicities include neutropenia, nausea, and vomiting. Interaction of Camptothecin Derivatives and Radiation Several investigators have reported that irinotecan enhances the cytotoxic effect of radiation in vitro and in vivo.[31,32] Omura et al[33] found that the cell kill was significantly enhanced when radiation was combined with the irinotecan derivative SN-38. The largest enhancement in cytotoxicity was seen when irinotecan was given just before or just after radiation therapy. Their data suggested that radiosensitization occurs by inhibition of potentially lethal damage repair.[33] Chen et al[34] showed that human MCF-7 breast cancer cells that were exposed to 20(S)-10,11 methylenedioxycamptothecin before or during radiation showed radiosensitization ratios of 1.6, while those treated with the drug after radiation showed substantially less enhancement of radiation-induced DNA damage. Kim et al also found greater radiosensitization when topotecan (Hycamtin) was administered 2 to 4 hours before radiation therapy compared to 2 hours after radiotherapy in the treatment of murine fibrosarcomas.[35] The radiobiology data imply that patients should be treated with a camptothecin derivative-based chemotherapy prior to or during their radiotherapy in order to derive full benefits of combined-modality therapy. Data also suggest that camptothecin derivatives including 9-nitro-20 (S)-camptothecin,[36] 9-aminocamptothecin,[37] and topotecan[38] are able to potentiate the tumoricidal effects of radiation. There are several hypotheses about mechanism of interaction between radiation and irinotecan. The first hypothesis suggests that the inhibition of topoisomerase I by camptothecin or its derivatives leads to the inhibition of repair of radiation-induced DNA strand breaks. The second hypothesis suggests that irinotecan or its analogs cause redistribution of cells into the more radiosensitive G2 phase of the cell cycle. The third hypothesis suggests topoisomerase I/DNA adducts are trapped by irinotecan at the sites of radiation-induced singlestrand breaks.[36] However, there is not sufficient evidence to identify the underlying mechanism with certainty. The predominance of the particular mechanism that is involved with radiosensitization may depend on which derivative of camptothecin is being used in combined-modality therapy. Irinotecan in Combination for NSCLC Basic principles used in the selection of chemotherapy drugs include nonoverlapping toxicities, differing mechanisms of action, and non-cross resistance.[39] Based on the above criteria, both preclinical and human data address the combination of cisplatin and irinotecan in lung cancer. Kudoh et al showed that in xenografts of the small-cell lung cancer (SCLC) tumor lines MNSUL and LX1, use of irinotecan in combination with cisplatin leads to a larger reduction in tumor size than either agent alone.[31] Early clinical studies in patients with advanced NSCLC have yielded favorable response rates in excess of 30%.[40] The combination of irinotecan and cisplatin has also been used in phase I and II clinical trials; early data from phase II studies revealed a 48% response rate in NSCLC[41] and 78% for SCLC.[42] Ueoka et al[43] reported a phase I trial with fractionation of both the cisplatin and irinotecan. Cisplatin (60 mg/m^2) was given on days 1 and 8 and escalating doses of irinotecan were given on the same days. Each cycle was repeated every 4 weeks. An impressive 78% response rate was seen in 18 patients with NSCLC.[43] A Vanderbilt-Ingram Cancer Center phase II trial looking at the combination of cisplatin at 80 mg/m^2 on day 1 and irinotecan at 60 mg/m^2 on days 1, 8, and 15 in 4-week courses with the possibility of escalating the irinotecan dose according to side effects was also undertaken.[44] The final irinotecan doses were modified to less than 40 mg/m^2 with a response rate of 29% in 52 patients. The median time to progression was 4.4 months, with a 1-year survival rate of 33%. Negoro et al[45] reported a randomized phase III trial in which the combination of irinotecan and cisplatin was compared to irinotecan alone or a cisplatin/vindesine combination. For stage IV patients, the irinotecan/cisplatin combination was superior to cisplatin/vindesine with respect to survival. Median survival times were 50.0 and 36.4 weeks, respectively. No significant difference in
survival time was seen between irinotecan/cisplatin and irinotecan alone. In addition, no significant difference in survival was seen in stage IIIB disease. However, the authors noted that no particular restriction was placed on chest irradiation in stage IIIB disease, which might have produced a heterogeneous group of IIIB patients. Masuda et al[46] reported a phase I study of docetaxel and irinotecan for stage IIIB and IV patients. Thirtytwo patients in the study were given escalating doses of docetaxel and irinotecan starting with 30/40 mg/m² given at 4-week intervals in 10-mg/m² increments until the maximum tolerated dose was reached. The maximum tolerated dose of docetaxel and irinotecan was 50/60 mg/m² or 60/50 mg/m². Neutropenia and diarrhea were the dose-limiting toxicities. There was a partial response of 37% with a median survival time of 48 weeks. The authors recommended 50 mg/m² of irinotecan on days 1, 8, and 15 and 50 mg/m² of docetaxel on day 2 given every 4 weeks for phase II trials. **Irinotecan and Radiotherapy for NSCLC** Combined-modality treatment relies on the ability of radiation and chemotherapy to simultaneously address both local and micrometastatic disease. An enhancement of local control is due to the radiosensitization effects of concurrent chemotherapy. In addition, concurrent chemotherapy addresses potential micrometastatic disease that local therapy, such as radiotherapy, cannot address adequately. Understanding the basic mechanisms of interaction of different drugs is also important to maximize the tumoricidal effects of chemotherapy while minimizing treatment-related toxicities. The optimal integration of irinotecan and cisplatin or other irinotecan-based chemotherapy integrated with thoracic radiotherapy is unclear. Evidence from previously completed trials addresses sequencing of chemotherapy and radiotherapy in combined modality for lung cancer. In the Cancer and Leukemia Group B (CALGB) 9130 trial, all patients received neoadjuvant platinum-based chemotherapy followed by radiotherapy with randomization to concurrent carboplatin (Paraplatin) with no improvement in survival, but there was a decreased local relapse rate.[47] The West Japan Lung Cancer Group has also compared concurrent and sequential combined-modality treatment in 314 patients with unresectable stage III NSCLC using a combination of mitomycin (Mutamycin), vindesine, and cisplatin chemotherapy. Their results show a doubling of 5-year survival rates (P = .03998) with concurrent treatment.[48] Curran et al reported results of the Radiation Therapy Oncology Group's RTOG 9410, which was a phase III, threearm trial comparing standard sequential chemoradiotherapy to two different concurrent arms.[13] The sequential arm used cisplatin at 100 mg/m² on days 1 and 29 with vinblastine at 5 mg/m² weekly * 5 with 60 Gy of thoracic radiotherapy following the chemotherapy. The second arm used the same chemotherapy with 60 Gy of thoracic radiotherapy starting on day 1. The third arm used cisplatin at 50 mg/m² on days 1, 8, 29, and 36, with oral etoposide at 50 mg/m² bid for 10 doses on weeks 1, 2, 5, and 6, with thoracic radiotherapy of 69.6 Gy at 1.2 Gy bid starting on day 1. Acute toxicity was higher with the concurrent treatment regimen, although late toxicities were not different between the arms. With median follow-up of 6 years, the arm with chemotherapy given concurrently with daily radiotherapy showed a median survival of 17 months (P = .046). The above trials support concurrent chemotherapy and radiotherapy for locally advanced NSCLC. Several phase I and II trials have administered irinotecan concomitantly with thoracic radiotherapy in stage III NSCLC (Table 1). Some trials added other chemotherapeutic agents to irinotecan. The response rates in these trials are in excess of 60%. These combinations appear to have reasonable acute toxicities; however, it is too early to assess the late complication rates. Takeda and colleagues examined the combination of escalating doses of weekly irinotecan with concurrent thoracic radiotherapy (60 Gy in 30 fractions over 6 weeks) in a phase II/III trial for locally advanced NSCLC.[49] They enrolled patients with stage III NSCLC who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and started irinotecan at 30 mg/m² intravenous weekly for 6 weeks. The maximum tolerated dose was 60 mg/m². At this dose level, five patients had grade 3/4 toxicity, two had grade 3 esophagitis, and three had grade 3/4 pneumonitis. The irinotecan dose for the phase II portion of the trial was 45 mg/m². A further 10 patients were treated at this dose level (17 total, including seven patients from phase I trial). One of the 10 patients in the phase II portion developed pneumonitis and died, while another patient developed grade 3 diarrhea. The overall response rate was 76.9%. After 22 months of follow-up, 1-year survival was 61.5%. Saka and colleagues performed a phase II trial in which 24 patients with locally advanced NSCLC were enrolled and received irinotecan at 60 mg/m² intravenous weekly * 6 with concurrent 60 Gy of thoracic radiation in 2-Gy/d fractions.[50] A total of 71% of patients received the planned chemotherapy, and 88% completed the planned radiotherapy with a partial response rate of 79%. Toxicities included three (12.5%) cases of grade 3 pneumonitis, two (8.3%) cases of grade 3 esophagitis, two (8.3%) cases of grade 3 neutropenia, and one (4.2%) case of a grade 3 fever. There were no grade 4 toxicities. Choy et al reported results of a phase I trial of weekly irinotecan 30 to 50 mg/m² and concurrent radiotherapy for unresectable stage III
The response rate was 58% among 13 treated patients. Nausea, vomiting, and esophagitis were the major toxicities. The maximum tolerated dose of concurrent chest radiation therapy and irinotecan was 40 mg/m$^2$ weekly for 6 weeks.

Kodoh and colleagues also performed a phase I/II trial of irinotecan and concurrent thoracic radiotherapy in locally advanced NSCLC. The maximum tolerated dose was 60 mg/m$^2$ with dose-limiting toxicities of esophagitis, pneumonitis, and diarrhea. Irinotecan/Platinum and Thoracic Radiation Therapy Platinum-based chemotherapy along with radiotherapy has been well established in the treatment of locally advanced NSCLC. The evaluation of irinotecan and concurrent thoracic irradiation has expanded to include the incorporation of the platinum compounds based on their known activity in NSCLC and preclinical data (Table 2).
Yokoyama and colleagues in the Japan Clinical Oncology Group (JCOG) conducted a phase I trial of 12 patients who received escalating doses of irinotecan and cisplatin with 60 Gy of thoracic radiation.[53] Six patients were able to receive the level 1 dose of 60 mg/m$^2$ of cisplatin and 40 mg/m$^2$ of irinotecan with their radiation. However, chemotherapy was discontinued before the planned three cycles were delivered in two patients. All patients completed the radiotherapy. At level 2 (60 mg/m$^2$ of cisplatin and 60 mg/m$^2$ of irinotecan), only three patients received all three cycles of chemotherapy. The three patients who did not complete chemotherapy also did not complete their radiotherapy. This group included one patient who died after the second course of chemotherapy. Due to the low intensity of irinotecan in levels 1 and 2 (irinotecan was often omitted on days 8 and 15 because of neutropenia or diarrhea) and the low radiation completion rate, the study was closed at level 2. There was an overall response rate of 67% (eight of 12 patients had a partial response). However, the overall survival rate at 1 year was only 33%. There have been two other reported Japanese trials of concurrent cisplatin, irinotecan, and radiation in NSCLC. Fukuda et al were able to give two courses of chemotherapy with split-course radiation. Irinotecan at 60 mg/m$^2$ on days 1, 8, and 15 and cisplatin at 80 mg/m$^2$ on day 1 was the recommended dose for this phase II study.[54] The overall response rate in 23 patients was 65%, with some cases of neutropenia, thrombocytopenia, and esophagitis. The Japanese Lung Cancer Group’s (JLCG) follow-up study of 68 patients involved induction cisplatin and irinotecan for two cycles followed by concurrent weekly irinotecan and thoracic radiation in patients with unresectable stage III NSCLC.[55] The significant toxicities were grade 4 neutropenia (6%), grade 3 esophagitis (4%), and grade 4 pneumonitis (2%). The response rate was 63.3%; the estimated 1-year survival was 71.7%. One other Japanese trial combined 60 Gy thoracic radiation in 30 fractions with carboplatin and irinotecan.[56] The 30 enrolled patients received carboplatin at 20 mg/m$^2$ daily for 5 days a week and intravenous irinotecan at 30 mg/m$^2$ weekly. Both drugs were repeated for 4 weeks and the dose of irinotecan was escalated from 30 mg/m$^2$ in 10-mg/m$^2$ increments. The maximum tolerated dose of irinotecan was 60 mg/m$^2$. The doselimiting toxicities were pneumonitis, esophagitis, neutropenia, and thrombocytopenia. Among the 30 patients, there were three complete responses and 15 partial responses, for an overall response rate of 60%. The median survival was 14.9 months and the 2-year survival rate was 34.2%. Oka et al[57] reported results from a phase I trial of irinotecan and cisplatin with concurrent split-course radiotherapy in patients with locally advanced stage III NSCLC. The overall response rate was 70%, with recommended doses for phase II study of an irinotecan (60 mg/m$^2$) and cisplatin (80 mg/m$^2$) combination. Similarly, Nakagawa et al[58] reported preliminary results using an irinotecan/carboplatin combination in unresectable stage III NSCLC patients with a response rate of 70% among 23 patients in the study. At the Vanderbilt-Ingram Cancer Center Affiliate Network, a phase II trial for patients with stage III unresectable NSCLC was conducted. The major goals of this study were to determine the maximum tolerated dose of irinotecan and carboplatin administered with radiation therapy, and to evaluate the toxicities of the combinations of irinotecan and radiation therapy and

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Radiation Therapy Dose</th>
<th>Topotecan Regimen</th>
<th>Acute Toxicity</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham[66]</td>
<td>12</td>
<td>60 Gy in 90 fractions</td>
<td>Days 1–5, 22–26, 0.5–1.0 mg/m$^2$</td>
<td>Neutropenia 17% (2/12) CR, Esophagitis, Nausea, Anorexia</td>
<td></td>
</tr>
<tr>
<td>Chachoua[67]</td>
<td>24</td>
<td>30–60 Gy in 10–35 fractions</td>
<td>Daily, 0.4 mg/m$^2$/d</td>
<td>Neutropenia 43% OR, Esophagitis 38% (9/24) PR, 25% (6/24) PD, 25% (6/24) SD</td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; PD = progressive disease; RT = radiation therapy; SD = stable disease.
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Irinotecan/carboplatin and radiotherapy. Other secondary objectives were to evaluate the response rate and response duration of advanced, medically inoperable and/or surgically inoperable NSCLC treated with the combination of irinotecan and local irradiation or the combination of carboplatin, irinotecan, and radiotherapy to the tumor masses.[59,60] The entry criteria for the trial required the patients to have NSCLC with unresectable stage III disease, including those with involved supraclavicular nodes with ECOG performance status 0 to 2 and less than 15% weight loss. In this trial, irinotecan was administered as an intravenous infusion, repeated every week for 6 weeks with a starting dose of 30 mg/m². Doses were planned for escalation at 10-mg/m² increments in successive cohorts of three patients. Thoracic radiotherapy was administered to the primary tumor and regional lymph nodes (40 Gy) followed by a boost to the tumor (20 Gy). The results of the first 18 patients entered onto this study through four dose escalations of irinotecan (from 30 to 50 mg/m² weekly, including the addition of carboplatin at an area under the concentration-time curve [AUC] of 2, with 30 mg/m² of irinotecan) were reported. One patient developed grade 5 esophagitis at the first dose level and the accrual was expanded to seven patients. No significant esophagitis was seen in the other six patients. At the second dose level of irinotecan (40 mg/m²/wk), one patient out of six experienced grade 2 esophagitis. At the third dose level of irinotecan (50 mg/m²/wk), two of three patients entered developed grade 4 nausea and vomiting, while two of the patients experienced grade 3 or 4 esophagitis. There were 10 partial responses and one complete response in 18 evaluable patients for a response rate of 61%. Nausea and vomiting as well as esophagitis were the main doselimiting toxicities. These preliminary data suggest that thoracic radiation can be combined with weekly irinotecan and carboplatin with acceptable toxicity, although results of higher doses are not yet available. The response rates and survivals seen in these phase I/II studies are encouraging and the toxicities associated with the use of thoracic radiation and concurrent irinotecan are acceptable. This treatment strategy needs to be compared with other combined-modality approaches in locally advanced NSCLC in randomized phase II or III trials. These promising results with tolerable toxicities in NSCLC should serve as a foundation to pursue the use of combination irinotecan and radiation in other disease sites as well. Ongoing randomized trials in other solid tumors will reveal additional information regarding the effectiveness of the combination of irinotecan and radiotherapy.

### Table 4

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Total Dose Radiation Therapy</th>
<th>Chemotherapy Regimen</th>
<th>Acute Toxicity</th>
<th>Response Rate</th>
</tr>
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<tbody>
<tr>
<td>Gray[72]</td>
<td>100 (43 LD/57 ED)</td>
<td>45 Gy in 25 fractions for LD</td>
<td>Paclitaxel Carboplatin Topotecan</td>
<td>Neutropenia Thrombocytopenia Fatigue</td>
<td>93% LD 88% ED</td>
</tr>
<tr>
<td>Oka[77]</td>
<td>17</td>
<td>60 Gy split 20 Gy x3</td>
<td>Irinotecan Cisplatin</td>
<td>Neutropenia Esophagitis Fatigue</td>
<td>94%</td>
</tr>
<tr>
<td>Kinoshita[78]</td>
<td>17</td>
<td>60 Gy in 30 fractions</td>
<td>Irinotecan Cisplatin</td>
<td>Fatigue</td>
<td>93.8%</td>
</tr>
</tbody>
</table>

CR = complete response; ED = extensive stage; LD = limited stage; PR = partial response; SCLC = small-cell lung cancer.

**Topotecan in Combined-Modality Therapy for NSCLC** In patients with previously untreated metastatic NSCLC, single-agent topotecan has yielded 0% to 15% rates, with the median survival duration of 30 to 40 weeks.[61-63] Perez-Soler et al[61] initially found that topotecan had an antitumor activity that...
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appeared to be more effective for squamous cell carcinoma (36% response rate, 5 of 14 patients) compared to adenocarcinoma (4% response rate, 1 of 26 patients). However, a follow-up phase II study[64] with 78 patients showed no significant difference between the histologies when considering response and survival end points. A randomized phase II trial of topotecan at 1.25 mg/m²/d * 5 every 3 weeks and cisplatin at 75 mg/m² on day 1 vs topotecan at 1.0 mg/m²/d * 5 every 3 weeks and paclitaxel at 190 mg/m² on day 1 showed response rates of 14% in the topotecan and cisplatin arm and 24% in the topotecan and paclitaxel arm.[65] Unfortunately, the results are not superior to other currently used combinations, and excessive toxicity occurred in the topotecan and cisplatin arm. In 1993, Graham et al[66] conducted a phase I trial of topotecan with concurrent radiotherapy for treatment of patients with locally advanced inoperable NSCLC (Table 3). Topotecan was administered by bolus infusion on days 1 to 5 and 22 to 26 at escalating doses: six patients received 0.5 mg/m², three patients received 0.75 mg/m² patients received 1 mg/m². Patients received thoracic irradiation to a total tumor dose of 60 Gy in 30 fractions. Twelve patients were enrolled and evaluable. At the dose level of 0.5 mg/m², none developed grade 4 hematologic toxicity; one of the six patients developed grade 3 esophagitis. At the 0.75 mg/m² dose level, two of the three patients developed grade 3/4 nonhematologic toxicity, which included anorexia, fatigue, nausea, vomiting, dysphagia, and weakness; none developed grade 4 hematologic toxicity. At the 1.0-mg/m² dose level, all three patients developed dose-limiting toxicities, including grade 3 esophagitis in one patient and grade 4 neutropenia in two patients. Thus, dose-limiting toxicity was exceeded at the 0.75 mg/m² level with concurrent thoracic radiotherapy. Median survival of all patients was 8.6 months. With a follow-up of 12 to 24 months, two patients were alive and free of disease, three patients were alive with disease (two with distant metastases and one with local disease and distant metastasis), and the remaining seven patients had died from their disease. Therefore, the investigators suggested that 0.5 mg/m² of topotecan ' 5 days for two cycles, concurrent with thoracic radiotherapy, was a tolerable regimen. While only phase I data, the overall survival in this trial was disappointing. Chachoua et al[67] conducted a phase I trial combining an escalating continuous intravenous infusion of topotecan at 0.4 mg/m²/d with escalating doses of concurrent thoracic radiotherapy in the treatment of 24 solid tumor patients (22 NSCLC, 1 breast, 1 mesothelioma) (Table 3). The radiotherapy dose and topotecan infusion duration were escalated in an alternating fashion through the dose levels. At the 60 Gy radiation dose, only NSCLC patients were eligible. Fifteen patients were able to complete the planned radiotherapy and topotecan infusion. Of the remaining nine patients, one patient was ineligible, four had hematologic toxicity, one progressed, one withdrew, and two discontinued therapy due to esophagitis. Nonhematologic toxicities included grade 3 esophagitis in two patients, grade 3 nausea/vomiting in one patient, and grade 3 fatigue in two patients. The overall response rate was 43%, and the thoracic radiotherapy at 60 Gy with topotecan at 0.4 mg/ m²/d for 42 days was recommended as the appropriate dose for future study by the authors. When considering the phase II studies of topotecan alone in advanced disease in combination with the phase I results of combined treatment in locally advanced disease, topotecan seems to have limited activity in NSCLC compared with other members of the "new" generation of chemotherapies, which includes irinotecan. Role of Topoisomerase I Inhibitors in SCLC Significant activity of topotecan with or without platinum-based agents in extensive-stage disease (ED) SCLC has been demonstrated.[68-70] Two phase II trials have reported approximately 37% response rates.[69,70] Therefore, topotecan makes an attractive agent to investigate in the limited- stage disease (LD) SCLC. One of the advantages of topotecan in SCLC is that it has the unique ability to cross the blood-brain barrier, making it active in the treatment of central nervous system (CNS) metastasis from SCLC. For example, Manegold et al[71] demonstrated, in a phase II study of topotecan in patients with SCLC and brain metastases failing first-line therapy, that of 16 evaluable patients, some of whom had previously received brain irradiation, four (25%) complete responses and six (38%) partial responses were observed. The objective response rate of CNS metastases was 63%. This finding is important for SCLC treatment, where CNS relapses can be high. The promising response rates in ED lead to investigations in LD SCLC patients (Table 4). Gray et al[72] conducted a phase II trial evaluating a three-drug regimen (paclitaxel/carboplatin/ topotecan) in the first-line treatment of limited-stage SCLC. Patients received four courses, and responders continued therapy with a further three courses of oral etoposide. Patients with LD SCLC received 45 Gy (1.8 Gy/d) to the chest beginning on week 6 of chemotherapy. A total of 100 patients were treated, including 43 LD and 57 ED patients. Eightyseven patients completed four courses of the paclitaxel/carboplatin/ topotecan combination. The response rates were 88% for ED patients and 93% for LD patients, for an overall response rate of 90%. However, the median survival for patients with LD was not reported. Single-agent irinotecan and the combination of irinotecan/cisplatin are
both active in the treatment of SCLC.[73-75] A phase III trial from the Japan Clinical Oncology Group showed that the combination of cisplatin and irinotecan had survival advantage over the traditional standard therapy of cisplatin and etoposide in ED chemotherapy-naive patients.[76] The irinotecan/cisplatin regimen had a median survival of 12.8 months, vs 9.4 months ($P = .002$) for the etoposide and cisplatin combination. The trial was stopped early because of the significant survival difference between the two groups. Because both irinotecan and cisplatin are known radiosensitizers, these agents may also be beneficial when combined with concurrent radiotherapy for the treatment of LD SCLC. Oka et al reported a phase I study of irinotecan and cisplatin with concurrent split-course radiotherapy in LD SCLC.[77] Chemotherapy consisted of four cycles of irinotecan on days 1, 8, and 15 and cisplatin on day 1, with 20 Gy radiotherapy at 2 Gy/d given on day 2 of each chemotherapy cycle for a total cumulative dose of 60 Gy to the chest. Three dose levels of irinotecan were 40, 50, and 60 mg/m$^2$ with a constant cisplatin dose of 60 mg/m$^2$. Of the 17 patients enrolled, 16 were evaluable. There were four patients with complete response, 11 patients with partial response, and 1 patient without change. The overall response rate was 94%. Irinotecan at 40 mg/m$^2$ with cisplatin at 60 mg/m$^2$ was recommended for phase II study. Kinoshita et al[78] conducted a phase I trial of escalating doses of irinotecan and a constant dose of cisplatin with concurrent thoracic radiotherapy (60 Gy) in patients with LD SCLC. Of the 17 patients enrolled, 16 were evaluable. Nearly all patients responded, with 4 complete responses and 11 partial responses, for an overall response rate of 93.8%. The investigators recommended that irinotecan be administered at 40 mg/m$^2$ in future studies, as two of four patients who received irinotecan 60 mg/m$^2$ discontinued therapy due to severe fatigue. The dose intensity of irinotecan at 50 mg/m$^2$ was only 49%. This data certainly suggests that this combination deserves further pursuit in a randomized phase II trial. **Newer Topoisomerase I Inhibitors** Phase II clinical trials of 9-aminocamptothecin and exatecan mesylate (DX-8951f) have tested the efficacy of these new topoisomerase I inhibitors in advanced NSCLC patients. 9-aminocamptothecin showed modest single-agent activity in NSCLC with an 8.6% response rate (5 partial responses out of 58 patients) and a median survival for the entire study group of 5.4 months.[79] Certainly its demonstrated radiosensitizing abilities[80] make 9-aminocamptothecin an attractive candidate for further study in earlier stages of disease. In another phase II trial, exatecan mesylate yielded an 18% overall response rate (3 partial responses out of 16 patients).[81] Using these phase II trials as a guide, it may be reasonable to pursue further study of these new topoisomerase I inhibitors in locally advanced NSCLC. **Conclusion** There has been improvement in outcomes of locally advanced NSCLC using combined-modality therapy. Concurrent chemoradiation approach has accumulated significant data to support its application in lung cancer. The response rates and survival rates with irinotecan and radiation in NSCLC from phase I/II studies are encouraging, and the toxicities associated with the use of thoracic radiation and concurrent irinotecan are manageable. This treatment strategy needs to be compared with other combined-modality approaches in locally advanced NSCLC in randomized trials. These results of combined radiation and topoisomerase I inhibitors in the treatment of lung cancer should also encourage the study of combination irinotecan and topotecan with radiation in other disease sites as well. The activity of irinotecan in colorectal cancers suggests that this could be an area in which to exploit the potential of irinotecan as a radiosensitizer. Ongoing trials are testing camptothecin derivatives with concurrent radiation in other solid tumors. The results of ongoing trials will provide a greater understanding in pursuit of optimal combined-modality therapy.

**Disclosures:** Dr. Choy has received research support from Aventis. He has served on speakers’ bureaus and acted as a consultant for Amgen, Bristol-Myers Squibb, AstraZeneca, Aventis, Pfizer, and Lilly. He has served on speakers’ bureaus for OSI, Genentech, and MedImmune.

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