Irinotecan in Combined-Modality Therapy for Locally Advanced Non-Small-Cell Lung Cancer

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The management of non-small-cell lung cancer is undergoing rapid evolution. Although the advent of combined-modality therapy has led to improved survival, most patients eventually succumb to the disease. The arrival of a

Introduction

Lung cancer is the leading cause of cancer-related morbidity and mortality. The estimated incidences for the year 2000 are 164,100 new cases and 156,900 deaths in the United States alone.[1] Five-year survival figures for lung cancer have remained in the 15% range from 1974 through 1995[1]; most of these cures involve early cancers usually treated with surgery alone. However, approximately 35% of patients present with locally advanced disease that is not amenable to surgical therapy, but is nonetheless potentially curable.[2] Traditional treatment with radiation alone in these patients has yielded low cure rates. This has spurred investigations of new methods to improve outcome.

Peckham and Steele outlined several possible mechanisms of interaction between radiation and chemotherapies: spatial cooperation, enhancement of tumor response, radioprotection, and nonoverlapping toxicities are all ways that chemotherapy and radiation may interact to improve therapeutic ratio.[3] Spatial cooperation describes a situation where disease located in a specific anatomic site is missed by one agent but treated by another. Enhancement refers to the administration of an agent that increases the effect of another agent, or when the effect of the combination is greater than would be expected with either agent alone. Radioprotection refers to the administration of a chemotherapeutic agent that would allow safe delivery of higher radiation doses.

Finally, toxicity independence, or nonoverlapping toxicities, describes when two partially effective agents can be used in combination without having to substantially reduce dose levels to avoid unacceptable side effects. Multiple phase III trials have shown benefits with the combined use of chemotherapy and radiation in the treatment of non-small-cell lung cancer at the expense of increased toxicity.[4-7] Overall, the meta-analysis from Pritchard et al suggests that traditional chemotherapy added to radiotherapy adds an average of 2 months to patient survival.[8]

Several new active agents that hold promise for improving outcome in lung cancer patients are emerging. These include paclitaxel (Taxol), docetaxel (Taxotere), vinorelbine (Navelbine), gemcitabine (Gemzar), and irinotecan (Camptosar, CPT-11), which have demonstrated response rates ranging from 20% to 54% as single agents in metastatic disease.[2] Finding a cure for this disease will require a better understanding of the mechanisms of action of these agents and their interactions with ionizing radiation, and the proper sequencing of these agents with other drugs and with radiation. This article will review the literature on the use of irinotecan in combination with thoracic irradiation in the treatment of non-small-cell lung cancer.

Mechanism of Camptothecin Activity

Camptothecin and its derivatives target DNA topoisomerase I, the DNA-relaxing enzyme.[9-12] This enzyme relaxes both positively and negatively supercoiled DNA, which allows diverse essential cellular processes, including DNA replication and transcription, to proceed. The key step for drug activity is stabilization of the topoisomerase I-DNA intermediate that the enzyme forms when cleaving DNA to allow for uncoiling to occur.[9-14] It is believed that collision between the drug-trapped topoisomerase-DNA complex and the replication material leads to G2-phase cell-cycle
Irinotecan is the prototype drug that was initially studied in the 1970s as a chemotherapeutic agent; however, its use was discontinued because of excessive toxicity. Ongoing research has begun to focus on camptothecin derivatives that have antineoplastic activity with improved toxicity profiles. This generation of drugs includes irinotecan. Irinotecan is a prodrug that is metabolized intracellularly to its active metabolite, SN-38, by a carboxylesterase-converting enzyme. This metabolite is more than 1,000 times more potent than irinotecan as an inhibitor of topoisomerase I. All of the camptothecins have a terminal lactone ring that can be hydrolyzed to a less active carboxylate species. Under acidic conditions, however, like that in the tumor microenvironment, the active lactone species is favored.

The plasma half-life of SN-38 after a short IV infusion is 10.2 hours (range: 5.9 to 13.8 hours), so that nanomolar concentrations of the drug persist for more than 2 days. This may affect its cytotoxicity. The major method of elimination of SN-38 is hepatic glucuronidation; a decreased ability to glucuronidate is thought possibly to correlate with increased gastrointestinal side effects. Clinically, the dose-limiting toxicity of irinotecan is delayed-onset diarrhea, which can be profuse and potentially life threatening. The diarrhea is thought to be related to the 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 release of the drug in the intestinal lumen. Other common toxicities include neutropenia, nausea, and vomiting.

**Interaction of Camptothecin and Radiation Therapy**

In planning combined-modality chemoradiotherapy, it is important to understand the mechanism of interaction between the two modalities. Several investigators have reported that camptothecin enhances the cytotoxic effect of radiation in vitro and in vivo. Omura et al assessed the radiosensitizing effects of SN-38 in HT-29 spheroids derived from a human colon cancer cell line. Results showed significantly enhanced cell kill with combined radiation and irinotecan; the largest gains in cytotoxicity occurred when irinotecan was administered just before or just after the radiation. The data also suggest that the mechanism of radiosensitization in the spheroids is through inhibition of potentially lethal damage repair.

Chen et al showed that camptothecin derivatives radiosensitized log-phased human MCF-7 breast cancer cells in a schedule-dependent manner. Essentially, cells exposed to 20(S)-10,11 methylenedioxy camptothecin before or during radiation had sensitization ratios of 1.6, while those treated with the drug after radiation had substantially less enhancement of radiation-induced DNA damage. The clinical implication of these results is that patients should be treated with camptothecin derivative-based chemotherapy prior to or during radiotherapy to receive the full benefits of combined-modality therapy. Emerging data also show that other camptothecin derivatives including 9-nitro-20(S)-camptothecin, 9-aminocamptothecin, and topotecan (Hycamtin) can potentiate the lethal effects of radiation.

There are several hypotheses, with varying amounts of supportive evidence, regarding the mechanism of interaction between radiation and irinotecan. The first hypothesis suggests that inhibition of topoisomerase I by camptothecin or its derivatives leads to inhibition of repair of radiation-induced DNA strand breaks. The second hypothesis suggests that camptothecin or its analogs causes redistribution of cells into the more radiosensitive G2 phase of the cell cycle. The third hypothesis is that topoisomerase I-DNA adducts are trapped by irinotecan at the sites of radiation-induced single-strand breaks, leading to their conversion into double-strand breaks. The primary mechanism involved with radiosensitization may depend on which camptothecin derivative is being used; there is currently insufficient evidence to identify the underlying mechanism with certainty.

**Irinotecan in Combined-Modality Therapy**

Combined-modality treatment relies on the ability of focused radiation and concurrent radiosensitizing agents to treat locally, while leaving the potential micrometastatic disease for...
chemotherapy to control. As such, it is also important to maximize the cytotoxic effects of chemotherapy while minimizing toxicities. This requires an understanding of the mechanisms of interaction between different drugs. Basic principles used in selecting drugs include nonoverlapping toxicities, differing mechanisms of action, and non-cross-resistance.[27] Based on these criteria, both preclinical and clinical trials have been undertaken to evaluate the cisplatin (Platinol)/irinotecan combination in lung cancer.

In xenografts of the small-cell lung cancer tumor lines Mnsul and LX1, Kudoh et al showed that irinotecan in combination with cisplatin led to a larger reduction in tumor size than either agent alone.[20] However, in xenografts of Mnqul, a cell line developed from human squamous cell lung carcinoma, combination cisplatin/irinotecan treatment was more effective than cisplatin alone but not more effective than irinotecan alone. According to the authors, the data clearly suggest that the combination of radiation and irinotecan should be effective in small-cell lung cancer; however, they cautioned that more data are needed, using a different non-small-cell lung cancer model, prior to concluding that the combination is better than irinotecan alone.

In patients with advanced lung cancer, early studies using irinotecan alone have yielded favorable response rates (> 30%).[28] The combination of irinotecan and cisplatin has also been assessed in phase I and II clinical trials; early data from phase II studies revealed a 48% response rate in non-small-cell lung cancer[29] and 78% in small-cell lung cancer.[30] A subsequent phase I trial looked at fractionation of both the cisplatin and irinotecan doses, ie, 60 mg/m of cisplatin and escalating doses of irinotecan were given on days 1 and 8. Cycles were repeated every 4 weeks. An impressive 78% response rate was seen in 18 patients with non-small-cell lung cancer.[31] A North American phase II trial examined the combination of cisplatin at 80 mg/m on day 1 and irinotecan at 60 mg/m on days 1, 8, and 15 in 4-week courses, with the possibility of escalating the irinotecan dose according to side effects.[32] The irinotecan dose was ultimately modified to less than 40 mg/m2; the response rate was 28.8% in 52 patients.

**Optimal Sequence of Chemoradiation**

The next issue in considering irinotecan in multimodality therapy for non-small-cell lung cancer is the optimal way to integrate irinotecan-based chemotherapy with thoracic radiotherapy, ie, the optimal sequence of chemoradiation. In the Cancer and Leukemia Group B (CALGB) 9130 trial, all patients received neoadjuvant platinum-based chemotherapy followed by radiotherapy and were randomly assigned to receive concurrent carboplatin (Paraplatin) or not. Results showed no improvement in survival with carboplatin added, but the relapse rate in the boost volume was decreased.[33] The West Japan Lung Cancer Group also compared concurrent and sequential combined-modality treatment in 314 patients. The 5-year survival rates were doubled in the group receiving concurrent treatment ($P = .04$).[34]

Results of the Radiation Therapy Oncology Group (RTOG) 9410—a phase III, three-arm trial comparing standard sequential chemoradiotherapy to two different concurrent arms[35]—was presented at the 9th World Conference in Lung Cancer in 2000. In the sequential arm cisplatin at 100 mg/m was administered on days 1 and 29 with vinblastine at 5 mg/m weekly × 5, and 60 Gy of thoracic radiotherapy following the chemotherapy. Patients in the second arm received the same chemotherapy with 60 Gy of thoracic radiotherapy starting on day 1. In the third arm, patients received cisplatin at 50 mg/m on days 1, 8, 29, and 36 with oral etoposide at 50 mg/m bid for 10 doses during weeks 1, 2, 5, and 6, and thoracic radiotherapy[69.6 Gy at 1.2 Gy bid starting on day 1.

Acute toxicity was higher in the concurrent treatment arm, although late toxicities were not different between the arms. With a median follow-up of 40 months, median survival in patients receiving concurrent chemotherapy and daily radiotherapy is 17 months ($P = .038$).[35] The compendium of these results thus suggests that concurrent chemoradiotherapy is a rational strategy to pursue in future trials.

**Irinotecan and Concurrent Radiation**

Several phase I and II trials have assessed concomitant administration of irinotecan and radiation in stage III non-small-cell lung cancer, with some trials adding other chemotherapy agents as well.
These combinations have resulted in encouraging response rates (> 60%) and appear to have reasonable rates of acute toxicities, although it is too early to comment on late complication rates (Table 1 and Table 2).

Takeda and colleagues examined the combination of weekly irinotecan at escalating doses with concurrent thoracic radiation (60 Gy in 30 fractions over 6 weeks) in a phase I/II trial.[36] Patients with stage III non-small-cell lung cancer and Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 began at an irinotecan dose of 30 mg/m² IV weekly for 6 weeks. There were dose-limiting toxicities found at 60 mg/m². At this dose level in five treated patients, there were two cases of grade 3/4 esophagitis and three cases of grade 3/4 pneumonitis. Therefore, the irinotecan dose for the phase II portion of the trial was 45 mg/m² and a further 10 patients were treated at this dose level (17 total, including 7 patients from the phase I portion). One of the 10 patients in the phase II portion developed pneumonitis and died, and another patient developed grade 3 diarrhea. The overall response rate was 76.9%, and 1-year survival rate was 61.5% after 22 months of follow-up.

Saka and colleagues conducted a phase II trial in which 24 patients with locally advanced non-small-cell lung cancer received irinotecan at 60 mg/m² IV weekly × 6 with concurrent thoracic radiation (60 Gy in 2-Gy fractions).[37] Among all 24 patients, 71% were able to receive the planned chemotherapy and 88% completed the planned radiotherapy. Partial responses were seen in 79% of patients. Toxicities included three cases of grade 3 pneumonitis, two cases of grade 3 esophagitis, two cases of grade 3 neutropenia, and one case of grade 3 fever. No grade 4 toxicities occurred. The investigators concluded that this was an active regimen in patients with non-small-cell lung cancer.

The evaluation of irinotecan and concurrent thoracic irradiation has expanded to incorporate platinum compounds as well, based on their activity in non-small-cell lung cancer, radiosensitizing abilities, and preclinical data.[20] In a phase I trial conducted from September 1994 to January 1995 by Yokoyama and colleagues in the Japan Clinical Oncology Group, 12 patients received escalating doses of irinotecan and cisplatin with 60 Gy of thoracic radiation.[38] Six patients were able to receive the level 1 dose of 60 mg/m² of cisplatin and 40 mg/m² of irinotecan with the radiation; however, chemotherapy was discontinued in two patients before the planned three cycles were delivered. All patients at dose level 1 completed the radiotherapy.

At dose level 2 (60 mg/m² of cisplatin and 60 mg/m² of irinotecan), only three of six patients received all three planned chemotherapy cycles. The three patients who did not complete chemotherapy also did not complete the radiotherapy; this included one patient who died after the second chemotherapy course.

Due to the low dose intensity of irinotecan in dose levels 1 and 2 (irinotecan was often omitted on days 8 and 15 because of leukopenia or diarrhea) and the low radiation completion rate, the study was closed at dose level 2. The overall response rate was 67% (8 of 12 patients had a partial response), but the overall survival rate at 1 year was only 33%. An ongoing phase I study at the Fox Chase Cancer Center may provide further insight into the tolerability of concurrent irinotecan, cisplatin, and thoracic radiation (see Table 1).[39]

Two other Japanese trials of concurrent cisplatin, irinotecan, and radiation in non-small-cell lung cancer have been reported. In a trial by Fukuda et al, patients received two courses of chemotherapy with split-course radiation (irinotecan at 60 mg/m² days 1, 8, and 15 and cisplatin at 80 mg/m² day 1 were the recommended doses for phase II study).[40] The overall response rate in 24 patients was 65%, with some cases of neutropenia, thrombocytopenia, and esophagitis.

The Japanese Lung Cancer Group’s follow-up study involved induction cisplatin and irinotecan for two cycles followed by concurrent weekly irinotecan and thoracic radiation.[41] The significant toxicities among 68 patients enrolled were neutropenia (6% of patients with grade 4), esophagitis (4% grade 3), and pneumonitis (2% grade 4). The response rate was 63.3% and the estimated 1-year survival rate was 71.7%. The authors concluded that induction chemotherapy followed by combined thoracic radiation and irinotecan was a promising treatment strategy for testing in randomized trials.

Another Japanese trial examined combining thoracic radiation (60 Gy) with carboplatin and
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The 30 enrolled patients received carboplatin at 20 mg/m² daily for 5 days a week and irinotecan IV weekly. Both drugs were repeated for 4 weeks and the irinotecan dose was escalated from 30 mg/m² in 10-mg/m² increments. The maximum tolerated dose of irinotecan was found to be 60 mg/m², and the dose-limiting toxicities were pneumonitis, esophagitis, neutropenia, and thrombocytopenia. Three complete and 15 partial responses were seen, for an overall response rate of 60%. The median survival has not been reached and the 2-year survival rate is 51.3%.

**VCCAN Phase I Trial**

The Vanderbilt Cancer Center Affiliate Network (VCCAN) has conducted a phase I trial involving patients with stage III unresectable non-small-cell lung cancer. The major goals of this study are to determine the maximum tolerated dose of irinotecan when administered with radiation therapy in patients with unresectable stage IIIA/IIIB non-small-cell lung cancer, to determine the maximum tolerated dose of irinotecan and carboplatin when administered with radiation therapy, and to evaluate toxicities of the combinations of irinotecan and radiation therapy and irinotecan/carboplatin and radiotherapy. Secondary objectives are to evaluate response rate and response duration of patients with advanced, medically inoperable and/or surgically inoperable non-small-cell lung cancer.[43,44]

Eligibility criteria for the trial included unresectable, stage III non-small-cell lung cancer, including involved supraclavicular nodes. Patients with malignant pleural effusions were excluded. Patients could not have had previous resection, chemotherapy, or radiotherapy, and only those with ECOG performance status of 0, 1, or 2 and < 15% weight loss were eligible. In this trial, irinotecan was administered as an IV infusion, repeated every week for 6 weeks. The weekly regimen was used to optimize the radiosensitizing properties of irinotecan. The starting dose was 30 mg/m² and doses were escalated at 10-mg/m² increments in successive cohorts of three patients (see Table 3).

Thoracic radiotherapy was administered concurrently to the primary tumor and regional lymph nodes (40 Gy) followed by a boost to the tumor (20 Gy). Preliminary results of the first 18 patients entered in the study through four dose escalations (from 30 to 50 mg/m² of irinotecan weekly including the addition of carboplatin at an area under the concentration-time curve of 2 with 30 and 40 mg/m² of irinotecan) are shown in Table 3. One patient developed grade 5 esophagitis at the first dose level and accrual was therefore expanded to seven patients. No significant esophagitis was seen in the other six patients. At the second dose level (40 mg/m²/wk), the worst toxicity was grade 2 esophagitis in one of six patients. At the third dose level (50 mg/m²/wk), two of three patients entered developed grade 4 nausea and vomiting, and two also experienced grade 3 or 4 esophagitis.

In 18 evaluable patients, 10 had a partial response and one had a complete response, for an overall response rate of 61%. These findings show that nausea and vomiting as well as esophagitis appear to be the main dose-limiting toxicities of concurrent weekly irinotecan and thoracic radiation in the outpatient setting. With the addition of carboplatin, leukopenia became a significant toxicity. These preliminary data suggest that thoracic radiation can be combined with weekly irinotecan and carboplatin with acceptable toxicity, although final results of higher doses are not yet available. The 1- and 2-year survival rates are encouraging.

**Conclusions**

The response and survival rates seen in these phase I/II studies are encouraging, and the toxicities associated with thoracic radiation and concurrent irinotecan are acceptable. This treatment strategy needs to be compared with other combined-modality approaches in locally advanced non-small-cell lung cancer in randomized phase II or III trials.

These promising results in non-small-cell lung cancer should also encourage the study of combination irinotecan and radiation in other disease sites as well. The Japanese phase I trial of irinotecan and cisplatin with concurrent thoracic radiotherapy in small-cell lung cancer yielded an impressive overall response rate of 93.8%. In another phase I trial in patients with locally advanced head and neck cancers, irinotecan was combined with docetaxel and conventionally fractionated radiation to yield a complete response rate of 75% and an overall response rate of...
The activity of irinotecan in colorectal cancer also suggests that this could be an area in which to exploit irinotecan’s potential as a radiosensitizer. As such, we hope to see trials testing irinotecan with concurrent radiation in other solid tumors, and we await results of ongoing randomized trials using irinotecan-based regimens in non-small-cell lung cancer.

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