Irinotecan in Combination With Radiation Therapy for Small-Cell and Non-Small-Cell Lung Cancer

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Lung cancer is the leading cause of cancer-related death in the United States. There was rapid progress in the treatment of lung cancer during past decades, but local control and survival rates are still poor.

Camptothecin is an alkaloid obtained from plants such as the Camptotheca acuminata tree. The target of camptothecin and its derivatives is topoisomerase I, an enzyme that relieves positive and negative supercoiling of DNA by cleaving a single DNA strand.[1-4] This drug binds the topoisomerase I/DNA complex and blocks religation of the cleaved strand, which inhibits DNA synthesis and results in cell death. X- or gamma-irradiation causes thousands of single-strand breaks per cell per gray. These sites are bound by topoisomerase I in the presence of camptothecin.[4] DNA/topoisomerase I/camptothecin cleavable complexes also affect the repair of potentially lethal damage in plateau-phase cells.[4] An additional mechanism of the synergistic effect of the combination of camptothecin and radiation therapy may be the synchronizing effect of irradiation itself, which preferentially kills G2- through M-phase cells and leaves camptothecin-sensitive S-phase cells.[5,6]

Irinotecan hydrochloride (CPT-11, Camptosar) is a semisynthetic water-soluble derivative of camptothecin. Irinotecan is a prodrug that is converted in vivo primarily by hepatic microsomal carboxylesterases to an active metabolite, SN-38. Substantial individual variability in irinotecan pharmacokinetics has been observed.[7] Irinotecan is active as a single agent in lung cancer treatment, producing response rates ranging from 11% to 34% in patients with advanced non-small-cell lung cancer.[8-11] Major toxicities of irinotecan are myelosuppression and early- or late-onset diarrhea, which are generally manageable.[12] Irinotecan showed potent radiosensitizing effects in human lung tumor xenografts which were related to the cell cycle.[13] However, the optimum timing of topoisomerase I inhibitor treatment for maximizing radiosensitizing effects remains controversial. Combination therapy with irinotecan/cisplatin has also been shown to cause significantly greater tumor regression (as compared with either agent alone) in small-cell and non-small-cell lung cancer xenografts in nude mice.[14] In addition, irinotecan and platinum agents are not cross resistant, and do not possess overlapping toxicity profiles.[15]

Non-Small-Cell Lung Cancer: Current Treatment Approaches

Lung cancer is the leading cause of cancer death in the United States in both men and women over 35 years old.[16] Depending on clinical circumstances, the principal treatment for stage III non-small-cell lung cancer includes radiation therapy, chemotherapy, surgery, and their combinations. The highest rate of cure for non-small-cell lung cancer has been achieved with surgery; however, fewer than 20% of non-small-cell lung cancer patients are considered candidates for surgical resection.[17] The 5-year survival rate with surgical resection for stage I/II non-small-cell lung cancer is 60% to 70%, but falls to 5% to 20% for stage III non-small-cell lung cancer.[18]

Radiation therapy to the primary tumor and regional lymph nodes has been the traditional treatment for locally advanced stage III non-small-cell lung cancer.[19] Although a complete response is rare, 5% to 10% of patients have a long-term survival benefit and palliation with standard fractionation to 60 Gy.[20]

A meta-analysis of 11 randomized clinical trials showed that cisplatin-based combinations plus radiation therapy reduced the risk of death by 10% compared with radiation therapy alone.[21] Therefore, a combined-modality approach has been standard.[22]
Studies have examined the optimal timing of chemotherapy relative to radiation therapy. For example, Furuse et al.[23] conducted a phase III study using cisplatin, vindesine (Eldisine), and mitomycin (Mutamycin) in addition to thoracic radiation therapy and showed superior response rate and median survival duration in patients receiving concurrent chemotherapy and radiation compared with those receiving sequential therapy. Another phase III study, conducted by the Radiation Therapy Oncology Group (RTOG), compared two concurrent chemotherapy and thoracic radiation therapy regimens to a standard sequential chemotherapy and thoracic radiation approach.[24] Preliminary results demonstrated a promising median survival rate for the concurrent platinum-based chemotherapy and radiation therapy arm.

Lung cancer is relatively chemotherapy resistant and new chemotherapeutic agents are needed, especially against non-small-cell lung cancer. Recently, many phase I and II studies have evaluated docetaxel (Taxotere), paclitaxel, gemcitabine (Gemzar), vinorelbine (Navelbine), and irinotecan with radiation.[25-28]

Concurrent Irinotecan and Radiation for Non-Small-Cell Lung Cancer

Concurrent Thoracic Radiation With Single-Agent Irinotecan

Several phase I/II trials of concurrent treatment with single-agent irinotecan and thoracic radiation therapy have been conducted in patients with locally advanced non-small-cell lung cancer (Table 1). An initial phase I study of the irinotecan/cisplatin combination with concurrent thoracic radiation therapy resulted in excessive diarrhea and myelosuppression.[29] Other trials demonstrated the feasibility of irinotecan/carboplatin (Paraplatin) with concurrent radiation.[30-32]

Kodoh and colleagues conducted a phase I/II trial of irinotecan administered weekly for 6 weeks and concurrent radiotherapy in locally advanced non-small-cell lung cancer.[32] Dose-limiting toxicities were esophagitis, pneumonitis, and diarrhea, and the maximum tolerated dose was 60 mg/m². In a phase II trial of the Japan Clinical Oncology Group (JCOG),[30] 24 eligible patients received irinotecan at 60 mg/m² weekly with 60 Gy of chest radiotherapy. The response rate was 79%, with pneumonitis and esophagitis as the major toxicities.

Takeda and colleagues examined escalating doses of weekly irinotecan with concurrent thoracic radiation.[28] The starting irinotecan dose was 30 mg/m² IV weekly for 6 weeks. The maximum tolerated dose was 60 mg/m²; at this dose level (n = 5), there were two cases of grade 3/4 esophagitis and three cases of grade 3/4 pneumonitis. A total of 17 patients received an irinotecan dose of 45 mg/m² (7 in the phase I portion and 10 in the phase II portion of the trial). Toxicities in the phase II portion (45 mg/m²) included fatal pneumonitis (n = 1) and grade III diarrhea (n = 1). Overall objective response rate was 76.9%, and 1-year survival rate was 62% with 22 months of follow-up.

Choy et al reported results of a phase I study of weekly irinotecan at 30 to 50 mg/m² and concurrent radiation therapy for stage III unresectable non-small-cell lung cancer.[33] Among 13 treated patients, 58% responded. Nausea, vomiting, and esophagitis were the major toxicities. The maximum tolerated dose of irinotecan is 40 mg/m² weekly for 6 weeks.

Concurrent Thoracic Radiation and Irinotecan/Platinum Combinations

The promising results achieved with irinotecan and concurrent thoracic radiation therapy led to incorporation of platinum compounds, which have demonstrated, in addition to antitumor activity, radiosensitizing effects in non-small-cell lung cancer (Table 2).[29,31,34-39] In a phase I trial of irinotecan/cisplatin plus radiotherapy in stage III non-small-cell lung cancer, conducted by Yokoyama and colleagues in the JCOG,[29] the response rate was 67%, but 1-year survival rate was only 33%.

Another Japanese trial of concurrent cisplatin, irinotecan, and radiation in non-small-cell lung cancer was reported by Fukuda et al, in which patients received two chemotherapy courses with split-course radiation.[34] The overall response rate in 23 evaluable patients was 65%, with some cases of
neutropenia, thrombocytopenia, and esophagitis. The Japanese Lung Cancer Group conducted a follow-up study with induction cisplatin and irinotecan for two cycles, followed by concurrent weekly irinotecan and thoracic radiation.[35] The significant toxicities were neutropenia (6% of patients with grade 4), esophagitis (4% grade 3), and hypoxia (2% grade 4). The response rate was 63%, and the estimated 1-year survival rate was 72%.

Another Japanese trial examined use of thoracic radiation with carboplatin and irinotecan.[36] Irinotecan was administered weekly, carboplatin was given at a dose of 20 mg/m$^2$ daily for 5 days a week, and both were repeated for 4 weeks. Radiation dose was 60 Gy in 2-Gy fractions for 6 weeks. The maximum tolerated dose of irinotecan was 60 mg/m$^2$, and dose-limiting toxicities were pneumonitis, esophagitis, neutropenia, and thrombocytopenia. The response rate was 60%, median survival has not been reached, but the 2-year survival rate was 51%. Oka and colleagues conducted a phase I study of irinotecan and cisplatin with concurrent split-course radiation therapy in patients with locally advanced stage III non-small-cell lung cancer.[37] Only one patient experienced a dose-limiting toxicity (neutropenia and diarrhea) at 60 mg/m$^2$ of irinotecan and 60 mg/m$^2$ of cisplatin. The response rate was 70%. Recommended doses for phase II study were 60 mg/m$^2$ of irinotecan and 60 mg/m$^2$ of cisplatin.

The regimen of weekly irinotecan/carboplatin with concurrent radiation therapy is likely to be adopted by RTOG as one treatment arm in a new randomized phase II trial in patients with locally advanced non-small-cell lung cancer.

Current Approaches to Small-Cell Lung Cancer

Small-cell lung cancer accounts for about 20% of new lung cancer diagnoses annually in the United States,[40] and one-third of those patients present with limited-stage disease confined to the chest. Combination chemotherapy and radiation therapy is the cornerstone of treatment. Median survival is limited to 15 to 20 months and the 2-year survival rate is 40% for patients with limited-stage disease who receive chemotherapy and radiation therapy.[41] The treatment goal for limited-stage small-cell lung cancer is the control of both local disease and distant metastases by using optimal chemotherapy and radiation therapy approaches. There are still unanswered questions with regard to combining chemotherapy and radiation therapy, including administration sequence, early vs late radiotherapy, and once-daily vs twice-daily radiation.

Takeda et al conducted a phase III study examining the sequence of chemotherapy (cisplatin plus etoposide) and radiation therapy in limited-stage small-cell lung cancer.[42] Median survival time was 31 months for patients receiving concurrent chemotherapy radiation and 21 months for those receiving sequential treatment. Murray et al also reported that in patients receiving concurrent chemotherapy/radiotherapy, early administration of thoracic radiation therapy (concurrent with the first cycle of etoposide/cisplatin, week 3) vs late administration (last cycle of etoposide/cisplatin, week 15) significantly improved median survival.[43]

Radiation therapy can be delivered once daily in larger fractions or twice daily in lower fractions. The multiple daily fractions result in less normal tissue damage, no radiobiological shoulder of small-cell lung cancer, redistribution of tumor cells between fractions, sublethal repair of normal tissue, and greater antitumor efficacy. Turissi et al reported results of once-daily vs twice-daily radiation therapy with four cycles of cisplatin and etoposide. Results showed that median survival was superior in the twice-daily arm (23 vs 19 months, $P = .04$).[44]

The optimal once-daily radiation dose in combined-modality therapy is unknown, although a dose of at least 50 Gy is probably necessary to control a tumor.[45] In a pilot study by Choi et al,[46] the maximum tolerated dose of twice-daily radiotherapy was 45 Gy given in 30 fractions over 3 weeks; in contrast, the maximum tolerated dose of daily radiation was 70 Gy in 35 fractions over 7 weeks. In this study, however, radiation treatment began at cycle 4 of chemotherapy.

The combination of cisplatin/etoposide has been the treatment of choice for limited-stage small-cell lung cancer.[42,47-51] Development of new drugs and more effective combination regimens is necessary for further improvement in outcome for small-cell lung cancer patients.
Irinotecan Containing Combinations and Thoracic Radiation for Limited-Stage Small-Cell Lung Cancer

Phase I and II trials of irinotecan have demonstrated clinical activity in patients with previously untreated and treated small-cell lung cancer.[28,50] Cisplatin, one of the most active drugs in this disease, is being combined with irinotecan and concomitant radiotherapy for treating patients with small-cell lung cancer.

Masuda et al reported a phase I study of irinotecan/cisplatin with concurrent radiation for limited-stage small-cell lung cancer.[52] The radiation dose was 60 Gy with conventional fractionation, and the cisplatin dose was 60 mg/m². Fatigue was the dose-limiting toxicity and the recommended irinotecan dose for the phase II study was 40 mg/m².

A phase I study conducted by Masuda et al of the irinotecan/cisplatin combination in patients with small-cell lung cancer showed antitumor activity with acceptable toxicity.[52] The radiation dose was 60 Gy with conventional fractionation, and the cisplatin dose was 60 mg/m² IV on day 1, every 28 days. Irinotecan was given on days 1, 8, and 15. In a subsequent phase II study, Kudoh et al assessed irinotecan plus cisplatin in patients with both limited-stage and extensive small-cell lung cancer.[14] Limited-stage patients received irinotecan at 60 or 80 mg/m² days 1, 8, and 15 and cisplatin at 60 mg/m² day 1 every 28 days for two courses. Responders received two additional chemotherapy courses followed by 50 Gy of thoracic irradiation. The overall response rate was 84% and the complete remission rate was 29%. Median survival time was 14.3 months, and the 2-year survival rate was 22%. Hematologic toxicity was the most common toxicity observed; nausea and diarrhea were the principal nonhematologic toxicities.

Noda et al conducted a phase III study comparing irinotecan/cisplatin vs etoposide/cisplatin for extensive small-cell lung cancer.[53] The study was terminated early due to a statistically significant survival difference at interim analysis favoring the irinotecan/cisplatin arm. The conclusion was that irinotecan plus cisplatin was an effective treatment for metastatic small-cell lung cancer.

Summary and Conclusions

Locally advanced non-small-cell lung cancer presents therapeutic challenges in terms of both local control and systemic treatment. The combination of chemotherapy and radiation therapy has resulted in improved outcome for such patients. Many phase I/II studies demonstrated the single-agent activity of irinotecan against advanced non-small-cell lung cancer, similar to that reported for other new active agents such as vinorelbine, gemcitabine, paclitaxel, and docetaxel. The synergistic effect of irinotecan and cisplatin was also observed in both in vitro and clinical studies, and phase I/II studies of radiation therapy and concurrent irinotecan and cisplatin demonstrated encouraging response and survival rates with acceptable toxicities. This regimen needs to be compared with other combined-modality approaches in locally advanced non-small-cell lung cancer in randomized phase II or III trials.

While irinotecan is a promising agent for use in combined chemotherapy and radiation therapy for advanced non-small-cell lung cancer, the best combination, dose, and timing of chemotherapy and radiation therapy remains unclear. Such patients should be encouraged to participate in the clinical trials.

Studies in patients with small-cell lung cancer have demonstrated that concurrent chemotherapy and radiation therapy is better than sequential chemotherapy and radiation therapy, early thoracic radiotherapy is better than late radiotherapy, and twice-daily radiation is better than once-daily treatment. The optimal radiation dose still needs to be defined for small-cell lung cancer. The cisplatin/etoposide combination is currently the standard chemotherapy for regimen for limited-stage small-cell lung cancer. Few clinical trials have evaluated combination chemotherapy including irinotecan with radiation for limited-stage small-cell lung cancer, thus trials are needed to explore the potential role of irinotecan for patients in this disease setting.
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