Weekly Irinotecan and Concurrent Radiation Therapy for Stage III Unresectable NSCLC

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In preclinical studies, the topoisomerase I inhibitor irinotecan (Camptosar, CPT-11) has demonstrated activity as a radiosensitizer, probably due to its ability to inhibit potentially lethal radiation damage repair. We conducted a

Introduction

Lung cancer is the leading cause of cancer death in the United States. Current projections indicate that 164,100 new cases will be diagnosed in the year 2000 while 156,900 deaths will occur.[1] Remarkably, although the incidence of lung cancer between 1999 and 2000 may decrease by approximately 10,000 cases, the mortality rate will decrease by less than 1% over the same time period. Because of the low cure rate, lung cancer kills more individuals than cancers of the breast, ovary, and colon combined and is, therefore, one of the major public health challenges for the next decade and beyond.

Previously, radiation alone was considered the standard of care for patients with unresectable non–small-cell lung cancer (NSCLC). Unfortunately, older series examining the role of radiation have not always demonstrated a survival advantage.[2,3] Instead, these poor results have led to the recent development of combined modality treatments, using more effective systemic therapy incorporating agents that have the potential for radiosensitization.

Large randomized studies have shown that concurrent chemotherapy and radiation is advantageous over induction chemotherapy prior to radiation.[4,5] There was also a significant effect on the rate of distant metastases in the patients receiving concurrent chemotherapy.[6,7] These studies have prompted both the American Society of Clinical Oncology[8] and the Ontario Lung Cancer Disease Site Group[9] to recommend combined modality therapy as the standard of care for good performance patients with locally advanced NSCLC.

A meta-analysis using data from 14 randomized trials and 2,589 patients found that the addition of chemotherapy to radiation reduced the risk of death at 2 years (relative risk 0.87; CI, 0.81 to 0.94).[10] This corresponded to a mean increase in life expectancy of 2 months. And, although there is a small benefit to the addition of chemotherapy to radiation, this must be balanced against the increased toxicity of combined modality treatment. Therefore, the investigation into combined modality therapy continues. However, the overall survival of patients with lung cancer remains unacceptably low. Clearly, new treatment strategies are needed.

Several newer chemotherapeutic agents are currently being combined with radiation in an attempt to improve both systemic and local control. These include vinorelbine (Navelbine), paclitaxel (Taxol), docetaxel (Taxotere), irinotecan (Camptosar, CPT-11), and gemcitabine (Gemzar). Each of these drugs produce single-agent response rates in the range of 15% to 25%, median survivals of 30 to 40 weeks, and 1-year survivals of 25% to 45%.[11] Phase II trials combining these agents with cisplatin (Platinol) or carboplatin (Paraplatin) yield outcomes superior to those of single-agent trials. Response rates are as high as 63%, median survival rates approach 1 year, and 1-year survival rates come close to 50% in the more promising studies.[12]

The identification of active new regimens in NSCLC is important for patients with advanced disease, but even more importantly, promising regimens with tolerable toxicity profiles may improve the cure rates in patients with early stage disease.

Preclinical Studies of Concurrent Irinotecan and Radiation
Irinotecan is a novel antineoplastic compound targeting DNA topoisomerase. Its mechanism of action appears to be in its interference with the topoisomerase I-mediated breakage-rejoining of DNA strands. In addition, irinotecan has demonstrated activity as a radiosensitizer in numerous preclinical studies, probably due to its ability to inhibit potentially lethal DNA damage repair.

The precise molecular mechanism of radiosensitization of drugs that target DNA topoisomerase I still remains to be defined. It is possible that stabilization of cleavable complexes by topoisomerase I inhibitors initiates radiosensitization. This drug-stabilized cleavable complex, with a conceded single-strand DNA break, may possibly be the cause of “potentially lethal” DNA damage. Interaction with undefined cellular processes such as DNA replication, RNA transcription, and DNA repair may transform such “potentially sublethal” DNA damage into “sublethal” DNA damage. It is plausible that such “sublethal” DNA damage could then be converted into “lethal” DNA damage with the addition of radiation-induced DNA damage.

Radiation sensitization with irinotecan has been reported in two human lung cancer xenografts. In these experiments, irinotecan was administered in nontoxic doses 1 hour prior to a single dose of irradiation. In other reports, radiation sensitization with a camptothecin derivative occurred when the drug was given either during or after irradiation. All of the topoisomerase I targeting drugs currently in clinical development are camptothecin derivatives. Among them, irinotecan, topotecan (Hycamtin), and 9-aminocamptothecin have undergone the most extensive clinical evaluation. A wide spectrum of clinical antitumor activity— including activity against colorectal, ovarian, small-cell and non–small-cell lung cancers, and malignant lymphomas—have been observed for these agents. Based on the single modality clinical activity observed for these agents, systemic chemotherapy for patients with metastatic cancers, and the preclinical activity demonstrated for these agents when combined with radiation, a number of clinical trials utilizing irinotecan with ionizing radiation have now been performed, primarily in patients with locally advanced NSCLC.

Clinical Studies of Concurrent Irinotecan and Radiation

In a clinical phase I/II trial conducted by Kudoh and colleagues that used escalating doses of weekly irinotecan with concurrent irradiation (60 Gy in 30 fractions over 6 weeks), the maximum-tolerated dose (MTD) of irinotecan was 60 mg/m² (administered by 90-minute intravenous infusion) when given weekly for 6 weeks. Dose-limiting toxicities (DLT) were observed at the 60-mg/m²/week dose level in the form of esophagitis, pneumonitis, and diarrhea. The recommended Phase II dose was 45 mg/m². Out of 24 evaluable patients, two achieved complete responses (CR); 16 achieved partial responses, for an overall response rate of 76%.[31]

A follow-up phase II trial was conducted in 24 previously untreated patients with unresectable stage IIIA/IIIB disease and good performance status. Their median age was 60 years (range, 44–72 years). In this study, Saka and colleagues evaluated irinotecan at 60 mg/m²/week with concurrent thoracic radiation (60 Gy in 30 fractions over 6 weeks). All six doses were delivered in 71% of patients; 21% were able to receive five of the six planned doses and 88% completed the course as planned. Partial responses were observed in 19 of 24 evaluable patients (79%). No patient experienced grade 4 toxicity. Grade 3 toxicities were observed in eight patients, including neutropenia (2), hypoxemia (3), esophagitis (2), and fever (1); no one experienced grade 3 or 4 diarrhea.[32]

Due to the intrinsic activity of the platinum agents against NSCLC, the radiation-sensitizing effect of platinum against a variety of solid tumors (including lung cancer), and the preclinical synergy demonstrated for platinum and irinotecan combinations in vitro, irinotecan with radiation is now being evaluated with regimens that integrate carboplatin. Nakagawa and colleagues treated 23 stage IIIA or IIIB patients with escalating doses of irinotecan plus a fixed dose of carboplatin (20 mg/m²) on a weekly basis for the first 4 weeks of radiation (60 Gy in 30 fractions over 6 weeks). At the time of the report, the irinotecan had been escalated from 30 to 50 mg/m²/week without the appearance of dose-limiting toxicity. Grade 3/4 diarrhea had been observed in only 2 of 23 patients (8.7%) and grade 3/4 pulmonary toxicity in 1 patient (4.3%). Objective responses were seen in 14 of the first 23 evaluable patients (60.9%).[33]

Recently, other Japanese investigators reported their experiences in a phase I study of irinotecan and carboplatin with concurrent thoracic radiotherapy for unresectable stage III disease. In their study, patients with stage IIIA or IIIB disease received weekly carboplatin at a dose of 20 mg/m² daily for 5 days per week with irinotecan from 30 mg/m² in increments of 10 mg/m². Radiation was administered at 60 Gy, in 2 Gy fractions, for 6 weeks. The MTD was 60 mg/m²; the dose-limiting
toxicities (DLT) included pneumonitis, esophagitis, neutropenia, and thrombocytopenia. Of 30 patients, 3 achieved a complete response and 15 a partial response, resulting in an overall response rate of 60%. The median survival has not yet been reached. At 55.5% and 51.3%, respectively, the 1- and 2-year survivals are impressive.[34]

In general, objective response rates were also impressive, with a range of 60% to 80% achieved in patients treated with various chemoradiation combinations with irinotecan and carboplatin. Severe treatment-related toxicities (grade 3 and higher) including fever, neutropenia, thrombocytopenia, pneumonitis, and esophagitis were rarely observed.

**Phase I Pilot Study**

A phase I pilot study of irinotecan, carboplatin, and thoracic radiation therapy for medically and/or surgically inoperable NSCLC is being conducted at the Vanderbilt-Ingram Cancer Center Affiliate Network (VICCAN). The primary objectives of this study are twofold: (1) to determine the MTD of irinotecan when administered with carboplatin and radiation therapy in patients with unresectable stage IIIA/IIIB NSCLC and (2) to evaluate the toxicities of the combinations of irinotecan and radiation therapy as well as those associated with the combination of irinotecan/carboplatin and radiotherapy. The secondary objectives are to evaluate the response rate and response duration of advanced medically inoperable and/or surgically inoperable NSCLC treated with the combination of irinotecan (± carboplatin) and local irradiation.

To be eligible for this study, patients are required to have histologically- or cytologically-documented unresectable stage IIIA or IIIB, an ECOG performance of 0 to 2, weight loss < 15% in the 3 months prior to diagnosis, and no prior chemotherapy or radiation therapy. Successive groups of three to six patients will receive progressively higher doses of irinotecan alone or with carboplatin in conjunction with fixed doses of radiotherapy. At least three patients in each group must be observed for DLT during the 6 weeks of therapy before subsequent patients can be enrolled at a higher dose level (Table 1).

Radiation therapy commenced on day 1 of the chemotherapy dose schedule. Chemotherapy was always given prior to radiation. The initial volume of the irradiated field, consisting of the tumor and mediastinum, received 40 Gy, at 2 Gy per fraction 5 days per week. This was followed by a boost to the primary and involved nodes of 20 Gy over 2 weeks, also administered in 2 Gy per fraction, 5 days per week. The initial treatment volume was treated with fields, which kept the maximum spinal cord dose at 45 Gy.

A total of 13 patients were entered into this study through three dose escalations (from 30 to 50 mg/m² weekly). At the first dose level, one patient developed grade 5 esophagitis, and accrual was expanded to seven patients. None of the six remaining patients at the first dose level experienced esophagitis. At the second dose level (40 mg/m²/week), the worst toxicity was grade 2 esophagitis in one patient. At the third dose level (50 mg/m²/week), two of three patients developed grade 4 nausea and vomiting. Additionally, grade 3 or 4 esophagitis occurred in two patients. Of the 12 evaluable patients, 7 achieved a partial response for an overall response rate of 58%.

In conclusion, nausea, vomiting, and esophagitis appear to be the principal DLTs of concurrent weekly irinotecan and thoracic radiation in the outpatient setting. The MTD of concurrent weekly irinotecan with thoracic radiation therapy appears to be 40 mg/m² weekly for 6 weeks. This study is still open to accrual at the second dose level (40 mg/m2) with the addition of carboplatin and thoracic radiation.[35] Concurrent radiation with weekly carboplatin and irinotecan has been adopted as one of the treatment arms in the new Radiation Therapy Oncology Group randomized phase II trial for patients with locally advanced non-small-cell lung cancer.

**References:**


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