Phase I Study of Induction Chemotherapy and Concomitant Chemoradiotherapy with Irinotecan, Carboplatin, and Paclitaxel for Stage III Non-small Cell Lung Cancer

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Background: The aim of this study was to determine the maximum tolerated dose (MTD), dose limiting toxicities (DLTs), and determine the phase II dose for the combination of irinotecan-carboplatin-paclitaxel given as induction chemotherapy and with concomitant chest radiotherapy for patients with Stage III non-small cell lung cancer.

Methods: Patients with Cancer and Leukemia Group B performance status of 0 to 2, stage IIIa and IIIB NSCLC patients with resectable or unresectable disease were treated with induction chemotherapy (irinotecan 100 mg/m², carboplatin AUC 5, and paclitaxel 175 mg/m² days 1 and 22) followed by concomitant chemoradiotherapy (irinotecan, carboplatin, and paclitaxel) and chest radiotherapy (66 Gy for unresectable and 50 Gy for resectable disease) beginning on week 7. The primary objective was to escalate the dose of irinotecan during chemoradiation in sequential cohorts to determine the DLT and MTD of the regimen.

Results: Thirty-eight patients were enrolled (median age 63 years, 57% male, 41% performance status 0, 30% resectable). Induction chemotherapy was tolerable and active (response rate 26%; stable disease 60%). Eight patients did not receive concurrent chemoradiotherapy because of progressive disease (5), death (1), hypersensitivity reaction to paclitaxel (1), and withdrawal of consent (1). Twenty-nine patients received concurrent chemoradiotherapy. The concomitant administration of chest radiotherapy with weekly irinotecan, carboplatin, and paclitaxel was not feasible at the first, second, and third dose levels. DLT was failure to achieve recovery to ≤ grade 1 absolute neutrophil count by the day of scheduled chemotherapy administration. Dose de-escalation was required for delivery of the regimen to irinotecan 30 mg/m², paclitaxel 40 mg/m² (with omission of carboplatin) delivered on weeks 2, 3, 5, and 6 of radiotherapy was the MTD. After induction chemotherapy, partial responses, stable disease, and progressive disease was observed in 26%, 60%, and 14% of patients, respectively. After chemoradiotherapy, partial responses were attained in 16 (55%) patients, whereas 12 patients (41%) attained disease stabilization. Median overall survival was 21 months for the entire cohort. Resectable patients had a median survival of 24 months, whereas unresectable patients had a median survival of 19 months. Differences in overall and progression-free survival rates between resectable and unresectable patients was not statistically significant (p = 0.52 and p = 0.90, respectively).

Discussion: Carboplatin, paclitaxel, and irinotecan with concurrent chemoradiotherapy was poorly tolerated as a result of neutropenia. Although dose de-escalation was required for delivery of the regimen, the response rates and survival outcomes were comparable to other similar regimens.

Key Words: Non-small cell lung cancer, Irinotecan, Radiation therapy, Multimodality therapy.

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Lung cancer remains the most common cause of cancer death in the United States. Approximately 20 to 30% of patients with non-small cell lung cancer (NSCLC) present with stage III disease. Much progress has been made in the treatment of stage III NSCLC over the past several decades with the development of multimodality therapy. Currently, concurrent chemoradiotherapy is the most effective management for inoperable Stage III NSCLC resulting in long-term overall survival in the range of 15 to 25%. Nevertheless, despite these advances in therapy, most patients succumb to the disease as a result of either locoregional or distant failure. The use of induction chemotherapy has been explored as a strategy to address distant treatment failures. Although the response rate to induction chemotherapy is approximately 30
to 40%, long-term survival remains unchanged.\(^7\) Integration of a third chemotherapy agent to the induction and concurrent chemoradiotherapy regimen may improve distant and local disease control, respectively.

Irinotecan, a derivative from the Camptotheca acuminata tree, inhibits DNA and RNA synthesis through DNA topoisomerase I inhibition.\(^1^1\) Preclinical data suggests synergistic relationships between the combination of irinotecan, carboplatin, and paclitaxel.\(^1^2–1^4\) Furthermore, irinotecan potentiates the cytotoxic effects of radiation therapy in tumor cell lines and tumor xenografts.\(^1^5–1^8\) The active metabolite of irinotecan, SN38, increases the proportion of cells in the G2-M and M phase. These cell cycle phases are the most sensitive to radiation injury.\(^1^6\)

Doublet\(^1^9,2^0\) and triplet\(^2^1,2^2\) irinotecan combinations were shown to be well tolerated and efficacious in metastatic NSCLC. Doses of irinotecan 100 mg/m\(^2\), paclitaxel 175 mg/m\(^2\), and carboplatin AUC 5 every 3 weeks can be safely administered together.\(^2^1\) This regimen achieved a response rate of 32% with a median time to progression of 5 months in patients with metastatic NSCLC.\(^2^2\) Irinotecan has also been combined with radiation therapy. Phase I studies determined the recommended Phase II dose of irinotecan to be 40 to 45 mg/m\(^2\)/wk with thoracic radiation therapy.\(^2^3,2^4\) Other investigators have combined irinotecan and platinum analogs during thoracic radiation therapy.\(^2^5,2^6\) In patients with unresectable stage III NSCLC, induction chemotherapy with carboplatin, paclitaxel, and irinotecan followed by concurrent carboplatin, paclitaxel, and radiotherapy was well tolerated and achieved a 1 year overall survival of 73%.\(^2^7\)

Based on the scientifically sound preclinical and promising clinical data of integrating irinotecan into existing NSCLC regimens, we conceived this phase I study in 1999 to evaluate the addition of irinotecan to carboplatin and paclitaxel during induction chemotherapy and during concurrent chemoradiotherapy. This phase I study aimed to determine the dose limiting toxicity (DLT) and the maximum tolerated dose (MTD) of irinotecan that could be administered in combination with paclitaxel, carboplatin with concomitant thoracic radiotherapy for stage III NSCLC. Here we report the results of our phase I trial with mature survival data.

**METHODS**

**Patient Selection**

Eligibility criteria included previously untreated, histologically or cytologically confirmed stage IIIA or IIIB NSCLC (1997 American Joint Committee on Cancer). Patients were excluded if they had a pleural effusion involving more than one third of the respective hemithorax or was cytologically positive. Additional eligibility requirements included Cancer and Leukemia Group B (CALGB) performance status (PS) of 0, 1, or 2 and measurable or evaluable disease.

Pretreatment staging evaluation included a complete history and physical examination, complete blood count, and complete metabolic panel. Prestudy radiographs included posterior-anterior (PA) and lateral chest x-rays, a chest computed tomography (CT) scan including the liver and adrenal glands, a head CT, and a bone scan. Surgical resectability was determined by thoracic surgeons before registration.

Laboratory measures required at study entry included white blood count >3500/\(\mu\)l; absolute neutrophil count (ANC) ≥1500/\(\mu\)l; hemoglobin >10 g/dl; platelet count >100,000/\(\mu\)l; blood urea nitrogen <1.5 times the institutional limit of normal; creatinine ≤1.5mg/dl or creatinine clearance ≥50 ml/min[Cockcroft]; bilirubin ≤1.5 times the institutional limit of normal; and serum glutamic-oxaloacetic transaminase <2 times the institutional limit of normal.

Patients were excluded if they had a serious medical or psychiatric illness which might complicate or interfere with chemotherapy or radiation administration, were taking phenytoin, phenobarbital, or other antiepileptic prophylaxis, or were pregnant or lactating. Patients could not have any additional active malignancy or malignancy within 3 years excluding nonmelanoma skin cancer. Patients were not permitted to have undergone previous chemotherapy or radiotherapy for NSCLC. Patients with a known history of Gilbert syndrome were excluded because these individuals may experience excessive irinotecan-induced toxicity.

All patients gave written, witnessed, and informed consent before study entry.

**Treatment**

**Induction Chemotherapy**

Induction chemotherapy consisted of two 21-day cycles of irinotecan, carboplatin, and paclitaxel (Figure 1). All three agents were given on days 1 and 22 as described by Socinski et al. Irinotecan was given at 100 mg/m\(^2\) intravenously over 90 minutes. Carboplatin was dosed at a target AUC of 5, and was given intravenously over 60 minutes. Paclitaxel was given at 175 mg/m\(^2\) intravenously over 60 minutes. Premedication before the administration of the chemotherapy con-
sisted of diphenhydramine 50 mg IV with famotidine 20 mg IV 30 minutes before paclitaxel. In addition, dexamethasone 20 mg IV and ondansetron 24 mg was given orally 30 minutes before the irinotecan. Routine prophylactic use of colony-stimulating factor was not allowed. Patients underwent response assessment after 2 cycles of induction chemotherapy and those with documented disease progression discontinued protocol therapy.

Concomitant Chemoradiotherapy

Concomitant therapy began on week 7 of protocol treatment. This phase I cohort study planned escalating doses of irinotecan and fixed doses of carboplatin and paclitaxel with concurrent chest radiotherapy. The initial schedule of drug administration (dose level 0) consisted of weekly doses of irinotecan 30 mg/m², carboplatin with AUC of 2, and paclitaxel 45 mg/m² (Figure 1 and Table 3). Because dose level 0 was not feasible because of dose limiting toxicities, for subsequent dose levels, carboplatin was omitted and chemotherapy paclitaxel and irinotecan were administered at a reduced dose and frequency as noted in the de-escalation schedule. Dose level −1 consisted of weekly infusions of irinotecan 30 mg/m² and paclitaxel 45 mg/m². Dose level −2 consisted of weekly doses of irinotecan 30 mg/m² and paclitaxel 40 mg/m². Dose level −3 consisted of irinotecan 30 mg/m² and paclitaxel 40 mg/m² given on weeks 2, 3, 5, and 6.

Radiotherapy

All patients underwent CT-based treatment planning with custom immobilization. All gross tumor and involved lymph nodes as seen on CT or positron emission tomography was included in the 66 Gy volume. Gross tumor was typically expanded by 1.5 to 2 cm to create a planning target volume. Treatment of uninvolved nodes was at the discretion of the treating oncologist. For patients who did not undergo surgical resection, the radiotherapy dose totaled 66 Gy in 2 Gy single daily fractions. For patients who were to undergo surgical resection, the radiotherapy dose totaled 50 Gy in 2 Gy single daily fractions. Total spinal cord dosage did not exceed 46 Gy. No dose limits were placed on normal lung, bone marrow, or heart.

Surgical Resection

Surgical resectability was determined by a thoracic surgeon at the time of registration. For surgically resectable candidates, a total radiation dose not exceeding 50 Gy was delivered, whereas for surgically unresectable candidates, a definitive radiotherapy dose of 66 Gy was administered. If surgical resection was feasible, patients were operated on after completion of induction chemotherapy and concurrent chemoradiotherapy. A CT scan was performed between week 4 and 5 of concurrent chemoradiotherapy to again determine the feasibility of surgical resection.

For patients who achieve a significant tumor response after induction chemotherapy, surgical resection may be considered before chemoradiotherapy, at the discretion of the medical oncologist and thoracic surgeon. If surgical resection was undertaken after induction chemotherapy, the chemoradiotherapy protocol (50 Gy) was resumed within 4 weeks after surgical resection.

Phase I Study Dose Escalation and Definition of MTD and DLT

The objective of this phase I study was to identify the DLTs and maximum administered dose (MAD) of irinotecan when administered in combination with paclitaxel, carboplatin, and concomitant chest radiotherapy. Toxicity was assessed continually throughout protocol therapy and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 2.0. DLT for concomitant chemoradiotherapy was defined as any of the following which occurred during the entire course of chemoradiotherapy: grade 4 thrombocytopenia or neutropenia, neutropenic fever, or need for platelet transfusion; ongoing myelosuppression ≥ grade 2 on any subsequent chemotherapy treatment day; grade 4 esophagitis; grade 4 vomiting or diarrhea despite maximal antiemetic or antidiarrheal support; all other ≥ grade 3 nonhematologic toxicities exceeding 7 days duration. Anemia, nausea, and alopecia were not considered dose-limiting.

According to the original design, a total of three to six patients were to be treated at any given dose of irinotecan. If DLT occurred in zero of three patients, we proceeded to the next dose level. If DLT occurred in one or two of three patients, a total of up to six evaluable patients were treated at that dose level, and if DLT occurred in two or fewer of the six patients, we proceeded to the next dose level. If DLT occurred in three of three patients, we stopped dose escalation and declared that dose level as the MAD. There would be no dose escalation beyond the MAD. If DLT occurred in greater than two of six patients, we stopped dose escalation and declared that dose level as the MAD. Doses were not escalated in individual patients. The recommended phase II dose will be one dose level below the MAD. Because dose level 0 was not feasible because of dose-limiting toxicities, the chemotherapy doses were reduced for subsequent dose levels, and the amended protocol stipulated dose de-escalation if >33% of patients treated at the initial dose level studied experienced a DLT. If dose de-escalation was required, the MTD would be defined as the highest dose level at which <33% of patients experienced DLT.

Dose Modifications

Dose modifications of irinotecan, carboplatin, and paclitaxel were specified for myelosuppression, nephrotoxicity, ototoxicity, nausea/vomiting, peripheral neuropathy, diarrhea, hepatic toxicity, and radiotherapy-related toxicities. The management of hematologic toxicities differed for the induction chemotherapy and concomitant chemoradiotherapy portions of treatment. Management of nonhematologic toxicities was identical for the induction chemotherapy and concomitant chemoradiotherapy portions of treatment. Filgrastim support was not allowed during the induction or concomitant chemoradiotherapy portion of treatment.

During induction chemotherapy, dose modification was based upon the blood counts on the day of chemotherapy treatment or observation of neutropenic fever on any day of
the cycle. For hematologic toxicity evident on a treatment day, the dose was modified accordingly: (1) if the ANC was 1000 to 1500/µl or platelets 50,000 to 74,000/µl, then irinotecan, carboplatin, and paclitaxel were reduced by 50%; (2) if the ANC was <1000/µl or platelets <50,000/µl, then all the chemotherapy was delayed until resolution to ≤ grade 2, then chemotherapy was to continue at 50% of the previous dose.

During concomitant chemoradiotherapy, for grade 4 ANC or platelets, chemotherapy and radiotherapy were delayed until resolution to ≤ grade 1, and then irinotecan, carboplatin, and paclitaxel were continued at 50% of the previous dose. For neutropenic fever, chemotherapy and radiotherapy were delayed until resolution to ≤ grade 2, and then irinotecan, carboplatin, and paclitaxel were continued at 50% of the previous dose. For grade 2 or 3 ANC or platelets, chemotherapy was delayed until resolution to ≤ grade 1, then irinotecan, carboplatin, and paclitaxel were continued at 75% of the previous dose. For grade 4 mucositis, stomatitis, esophagitis, dermatitis or other in-field radiotherapy related toxicity during radiotherapy or on day 1 of any treatment week, chemotherapy and radiotherapy were delayed until resolution of toxicity to ≤ grade 3, then irinotecan, carboplatin, and paclitaxel were continued at 50% of the previous dose. If grade 4 vomiting occurred despite aggressive antiemetic prophylaxis, the carboplatin and irinotecan doses were decreased by 50% for subsequent cycles. If grade 2 neurotoxicity developed, patients were retreated upon recovery to grade 1 toxicity with a 25% dose reduction of carboplatin and paclitaxel. If grade 3 neurotoxicity developed, carboplatin and paclitaxel were discontinued. For all other toxicities ≥ grade 3 (except alopecia, lymphopenia, and anemia), chemotherapy and radiation therapy was held until resolution to ≤ grade 1, then reinstituted, at a 25% dose reduction of irinotecan, carboplatin, and paclitaxel.

### Assessment of Response and Toxicity

Patients were assessed with regard to safety and tolerability using the National Cancer Institute Common Terminology Criteria for Adverse Events 2.0. Tumor response was defined using the World Health Organization Tumor Response Criteria. Patients were to be evaluated for response 9 to 11 weeks after the initiation of therapy and then approximately 1 month after the completion of concomitant chemoradiotherapy or as otherwise clinically indicated.

### Statistical Analysis

Response rates (complete and partial responses) were computed and exact 95% confidence intervals (CIs) were constructed based on the binomial distribution. Progression-free survival (defined as the interval between the first day of therapy and disease progression or death from any cause) and overall survival (defined as the interval between the first day of therapy and death from any cause) curves were estimated for all enrolled, eligible patients using the Kaplan-Meier method. CIs for the median survival times were obtained as described in Brookmeyer and Crowley. Survival rates were compared between groups using the log-rank test.

### RESULTS

#### Patient Selection and Characteristics

Between December 1999 and November 2003, a total of 38 patients enrolled in the study (Table 1). One patient enrolled on the study and received the intended therapy but on retrospective review was found to have metastatic disease at the time of enrollment. This patient was excluded from all analyses.

| Characteristic | Total enrolled | Values
<table>
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<tbody>
<tr>
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<td>Male</td>
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</tr>
<tr>
<td>Female</td>
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<tr>
<td>Race</td>
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</tr>
<tr>
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<tr>
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<td>1</td>
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<td>2</td>
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<td>Histology</td>
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<td>Stage</td>
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<tr>
<td>IIIB</td>
<td>24 (65)</td>
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</tr>
<tr>
<td>Weight loss</td>
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<tr>
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</tr>
<tr>
<td>Less than 10%</td>
<td>8 (22)</td>
<td></td>
</tr>
<tr>
<td>Greater than 10%</td>
<td>4 (11)</td>
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</tr>
<tr>
<td>Resectable</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (30)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26 (70)</td>
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*Values in parenthesis indicate percentage values. One patient enrolled on the study and received the intended therapy but on retrospective review was found to have metastatic disease at the time of enrollment. This patient was excluded from all analyses.*
TABLE 2. Toxicities Associated with Induction Chemotherapy

<table>
<thead>
<tr>
<th>Toxicities, (n = 36)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
<td>Hematologic toxicities</td>
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<td></td>
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<tr>
<td>Leukocytes</td>
<td>8 (22)</td>
<td>13 (36)</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>ANC</td>
<td>5 (14)</td>
<td>9 (25)</td>
<td>9 (25)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>16 (44)</td>
<td>14 (39)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>10 (28)</td>
<td>1 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-hematologic toxicities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td>2 (6)</td>
<td>2 (6)</td>
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<tr>
<td>Fever/infection</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Non-neutropenia infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>22 (61)</td>
<td>7 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (47)</td>
<td>5 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (31)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (47)</td>
<td>6 (17)</td>
<td>1 (3)</td>
<td></td>
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<tr>
<td>Constipation</td>
<td>11 (31)</td>
<td>2 (6)</td>
<td></td>
<td></td>
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<tr>
<td>Neupathy</td>
<td>6 (17)</td>
<td>1 (3)</td>
<td></td>
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<tr>
<td>Creatinine</td>
<td>1 (3)</td>
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<td></td>
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<tr>
<td>Mucositis</td>
<td></td>
<td></td>
<td>2 (6)</td>
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</tr>
<tr>
<td>Esophagitis</td>
<td>1 (3)</td>
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</table>

Induction Chemotherapy: Toxicity and Response

One patient developed a hypersensitivity reaction to paclitaxel during the first cycle of induction chemotherapy and discontinued protocol therapy. As a result, 36 patients were considered fully assessable for safety associated with the use of all three induction chemotherapy agents. Seventy-one cycles of induction chemotherapy were administered. Four patients experienced myelosuppression (one patient with grade 3 neutropenia and three patients with grade 4) and required dose modification of the second cycle of induction chemotherapy.

Induction chemotherapy toxicities are listed in Table 2. Significant toxicities for patients were mainly hematologic. Grade 3/4 leukopenia and neutropenia occurred in four (12%) and 17 (47%) patients, respectively. Neupropenic fever and non-neutropenic infections each occurred in two patients (6%). Grade 3/4 diarrhea and grade 3/4 vomiting each occurred in one patient (3%). The most common nonhematologic toxicity was fatigue, which occurred in 80% of patients.

Thirty-five patients were assessable for response to induction chemotherapy. One patient developed a hypersensitivity reaction to paclitaxel and was treated off protocol. Another patient developed acute liver failure secondary to alcohol cirrhosis after cycle 1 and did not receive further study therapy. Partial responses were observed in nine of the 35 assessable patients (26%; 95%CI, 12%–43%). Twenty-one (60%) had stable disease. Five patients (14%) developed progressive disease after induction chemotherapy. Of the five patients with progressive disease, two had local disease progression and three developed distant metastases to the skin, liver, and retroperitoneum, respectively. Of the two patients with local disease progression, one patient had tumor invasion into the heart ventricle and no further therapy was administered, whereas another patient was taken off protocol and given chemoradiotherapy.

Concurrent Chemotherapy and Radiotherapy

Phase I Dose Escalation and Determination of MTD

Twenty-nine patients (22 unresectable and seven resectable) received concurrent chemoradiotherapy and all were evaluable for toxicity (Table 3). Eight patients did not receive concurrent chemoradiotherapy because of progressive disease (five patients), death from decompensated alcohol cirrhosis (one patient), hypersensitivity reaction to paclitaxel (one patient) and withdrawal of consent (one patient).

A total of 163 cycles of chemoradiotherapy were administered and the median number of cycles per patient was six (range 4–6). For patients with resectable tumors (n = 7), a total of 33 cycles were administered and the median number of cycles per patient was five (range 4–5). For patients with unresectable tumors (n = 22), a total of 130 cycles were administered and the median number of cycles per patient was six (range 5–6).

There were no treatment-related deaths. DLT occurred in 12 patients and failure to achieve recovery to ≤ grade 1 ANC by the day of scheduled chemotherapy administration was the predominant DLT occurring in 10 patients. All four patients in the first dose level (dose level 0) experienced DLT. Three out of six patients (50%) in dose level −1 experienced DLT. Further dose de-escalation was required because four out of 10 patients (40%) experienced DLT in dose level −2. DLT at dose level −2 was grade 3 pneumonia (one patient), grade 3 angina (one patient) and failure to achieve recovery to ≤ grade 1 ANC by the day of scheduled chemotherapy administration (two patients). At dose level −3, only one patient (11%) experienced DLT. Therefore, the MAD was dose level 0, and the MTD was dose level −3.

TABLE 3. Treatment Dose Levels and Dose Limiting Toxicities (DLT)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>n</th>
<th>Irinotecan (I); Paclitaxel (P); Carboplatin (C)</th>
<th>Median Radiation Dose (Range)</th>
<th>No. of Patients with DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>I 30 mg/m²; P 45 mg/m² weekly; C AUC = 2</td>
<td>6400 (5000–7000)</td>
<td>4</td>
</tr>
<tr>
<td>−1</td>
<td>6</td>
<td>I 30 mg/m² weekly; P 45 mg/m² weekly; C</td>
<td>6533 (5000–7000)</td>
<td>3</td>
</tr>
<tr>
<td>−2</td>
<td>10</td>
<td>I 30 mg/m² weekly; P 40 mg/m² weekly; C</td>
<td>6511 (5000–7400)</td>
<td>4</td>
</tr>
<tr>
<td>−3</td>
<td>9</td>
<td>I 30 mg/m² weeks 2, 3, 5, 6; P 40 mg/m² weeks</td>
<td>6500 (5940–7020)</td>
<td>1</td>
</tr>
</tbody>
</table>

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There were no grade 4 toxicities observed at any dose level. At the dose level $/H_{11002}3$, the recommended phase II dose, no grade 3 hematologic toxicities were observed. Grade 1/2 anemia, leucopenia, neutropenia, and thrombocytopenia occurred in 89%, 33%, 22%, and 22% of the nine patients, respectively. The only grade 3 nonhematologic toxicity was esophagitis occurring in 11% of these patients. Among all 29 patients, nonhematologic grade 1/2 toxicities included the following: fatigue (86%), nausea (48%), diarrhea (24%), and vomiting (17%).

Response to Concomitant Chemoradiotherapy

Of the 29 patients who underwent chemoradiotherapy, one patient (3%) was found to have brain metastasis at the completion of therapy (Table 5). Partial responses were attained in 16 (55%; 95% CI, 36–74%) patients whereas 12 patients (41%) attained disease stabilization.

Eleven patients were initially thought to be surgically resectable, but only six patients underwent thoracotomy, of which two patients had pathologic complete responses, two had microscopic residual disease, and two had gross residual disease. One of the patients who had brain metastasis at the completion of therapy underwent thoracotomy for palliation of chest wall pain.

Survival

The median length of follow-up for all 37 patients was 20.6 months (range 1.1–78.0). Twenty-five of the 37 eligible patients have died. Among the 12 survivors, the median length of follow-up was 68.3 months (range 35.0–78.0).

Median overall survival was 20.6 months (95% CI, 11.0–40.7 months) for the entire cohort (Figure 2A). The median progression-free survival time was 7.6 months (95% CI, 5.8–22.8 months) for the entire cohort (Figure 2B). For patients deemed resectable at registration, median overall survival was 24.4 months (95% CI, 1.9–∞). For patients deemed unresectable, median overall survival was 18.8 months (95% CI, 10.9–40.7) (Figure 2C). Median progression-free survival for resectable patients was 13.7 months (95% CI, 1.2–∞). The median progression-free survival time for unresectable patients was 7.6 months (95% CI, 5.8–29.2) (Figure 2D). The differences in overall and progression-free survival rates between resectable and unresectable patients were not statistically significant ($p = 0.52$ and $p = 0.90$, respectively).

Pattern of Failure

As of the last follow up, 12 (32%) out of 37 patients were alive. Ten patients were alive without evidence of disease whereas seven had died without evidence of recurrence. Twenty patients (54%) out of the 37 developed disease progression. Six of these patients (30%) experienced local failure, 11 (55%) developed distant metastases, and three patients (15%) developed disease recurrence locally and at distant sites. Seven patients developed central nervous system metastases as the site of first relapse.

Long-term Complications and Sequelae

Four out of the 29 patients (14%) who underwent chemoradiotherapy developed an esophageal stricture and required an esophageal dilation procedure on at least one occasion. One patient developed a second primary lung cancer outside the radiotherapy field, and another patient developed a malignant thymoma.

**DISCUSSION**

The aim of the present investigation was to evaluate the feasibility, toxicity, and safety of an intensive chemoradiotherapy-
apy protocol in patients with stage III NSCLC. Based on our results, it was not feasible to administer carboplatin, paclitaxel, and irinotecan concurrently with chest radiation therapy because of dose-limiting neutropenia. The regimen was feasible only after omission of carboplatin and reduction of doses to irinotecan 30 mg/m² and paclitaxel 40 mg/m² delivered on weeks 2, 3, 5, and 6 with concurrent daily chest radiotherapy.

This study was performed during a time when knowledge of irinotecan metabolism by uridine diphosphoglucuronosyltransferase 1A1 polymorphism was still in its infancy. The contribution of such polymorphisms to the toxicities observed in our trial is unknown. One may hypothesize that the tolerability of irinotecan may be better if patients were genotyped and dosed accordingly. Regardless, the results of this phase I trial show that the concurrent chemotherapy regimen of irinotecan, carboplatin, and paclitaxel was poorly tolerated and was only feasible with the omission of carboplatin and significant dose de-escalations. Therefore, we do not recommended that this regimen be investigated further. Nevertheless, several important observations need to be highlighted.

Firstly, despite significant dose de-escalations, the chemoradiotherapy regimen utilizing for the most part irinotecan and paclitaxel attained a long-term 5-year overall survival rate of approximately 30% (95% CI, 17–46%). Even for patients who were deemed unresectable at registration (n = 26), their 5-year survival was 25% (95% CI, 10–43%). These survival figures seem similar to those achieved by other established chemoradiotherapy regimens, but this comparison must be made in light of our small number of patients and the lack of statistical power. Furthermore, the contribution of the triplet induction regimen to this survival improvement is unclear. Secondly, there seems to be a trend toward better survival in the surgically resectable patients. This observation, based on a small number of patients and not statistically significant, is consistent with the current literature. Recently however, the North American Intergroup Trialists showed that surgical resection after chemoradiotherapy did not significantly improve treatment outcome over chemoradiotherapy alone. In addition, the approach of using induction chemotherapy followed by surgical resection also did not improve overall survival over chemotherapy followed by radiotherapy. Therefore, although surgically resectable patients may have a better outcome, the role of surgery after induction chemotherapy or chemoradiotherapy is questionable.

FIGURE 2. A: Overall survival in all eligible patients, B: Progression-free survival in all eligible patients, C: Overall survival by Resectability Status (resectable --- dashed line, unresectable — solid line) at time of diagnosis, D: Progression-free survival by Resectability Status (resectable --- dashed line, unresectable — solid line) at time of diagnosis.
Thirdly, the response rate after induction chemotherapy with the triplet regimen was 26% (95% CI, 12–43%) in the 35 assessable patients. Compared with induction chemotherapy with carboplatin-paclitaxel in CALGB 39801, with a response rate was 31%, the efficacy of the triplet induction regimen seems similar. This is paradoxical to what is known in the metastatic setting, whereby a triplet regimen improves response rates but not overall outcome. Finally, late esophageal toxicity, as opposed to acute esophageal toxicity is relatively uncommon. In a review across several combined modality Radiation Therapy Oncology Group trials, the late esophageal toxicity rates with sequential chemotherapy and radiotherapy was 2.2%, and almost doubled with the use of induction chemotherapy followed concurrent chemoradiotherapy (3.6%). The rate of late esophageal toxicity observed in our patients is higher compared with these reports. Nevertheless, it is unlikely that the chemotherapy regimen was the cause of this because patients who developed the late toxicities were in the lower dose levels.

An interesting feature of our trial is the inclusion of patients who have poor-risk factors—greater than 10% weight loss and PS 2. We accrued three patients with PS 2, three patients with weight loss >10% and one patient with both these poor-risk factors. Most chemoradiotherapy trials in NSCLC have excluded patients with poor-risk factors. In trials specifically evaluating this population of patients, the carboplatin-etoposide with concurrent radiotherapy regimen seems well tolerated. In our trial, four of these seven patients completed the prescribed regimen. The other three patients developed progressive disease after induction chemotherapy and did not receive chemoradiotherapy. Nevertheless, it is important to note that the poor-risk factor patients who completed their regimens were not in dose level 0 where they would have received all three chemotherapies. Although this concurrent chemoradiotherapy is feasible in poor-risk patients not all such patients are equivalent and the optimal chemoradiotherapy approach for these patients remains to be defined.

Because this trial was conceived in 1999, the management of Stage III NSCLC has evolved. One significant change occurred with the reporting of the CALGB 39801 study. This study randomized unresectable stage III NSCLC patients to either immediate concomitant carboplatin-paclitaxel with radiotherapy or two cycles of induction chemotherapy with carboplatin and paclitaxel followed by identical concomitant chemoradiation, and it found that the survival outcomes between the two groups were no different. In light of the CALGB 39801, concomitant chemoradiotherapy is currently considered the standard approach for patients with unresectable NSCLC and a good PS.

A second major impact on the treatment of unresectable stage III NSCLC came with the reporting of SouthWest Oncology Group (SWOG) 9504 and a subsequent randomized trial by the Hoosier Oncology Group. The use of concurrent chemoradiotherapy followed by consolidation chemotherapy, as pioneered by SWOG 90194 and later optimized in SWOG 9504, has been adopted as a standard approach for unresectable stage III NSCLC. The Hoosier Oncology Group evaluated the role of consolidation chemotherapy and found that there was no significant difference in survival between the group that received consolidation docetaxel and those who did not. Therefore, concomitant chemoradiotherapy remains the standard approach for unresectable stage III NSCLC.

Future investigations of multimodality management of NSCLC should include novel targeted therapies, such as tyrosine-kinase inhibitors. Nevertheless, the promise of targeted therapies must be explored carefully and rationally because the incorporation of such therapies may lead to detrimental outcomes such as in SWOG 0023. As far as the incorporation of irinotecan to chemoradiotherapy, we found that a triplet chemoradiotherapy regimen was not feasible. Nevertheless, even with several dose de-escalations, the irinotecan-based chemoradiotherapy for stage III NSCLC seems efficacious. As the field of stage III NSCLC moves forward, the role of irinotecan-based radiosensitizing-dose chemoradiotherapy may be limited because the focus of investigations has shifted to improving outcomes of full-dose concurrent chemoradiotherapy with consolidation regimens.

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REFERENCES


