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CLINICAL INVESTIGATION **Lung**

A PHASE I/II RADIATION DOSE ESCALATION STUDY WITH CONCURRENT CHEMOTHERAPY FOR PATIENTS WITH INOPERABLE STAGES I TO III NON-SMALL-CELL LUNG CANCER: PHASE I RESULTS OF RTOG 0117

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Purpose: In preparation for a Phase III comparison of high-dose versus standard-dose radiation therapy, this Phase I/II study was initiated to establish the maximum tolerated dose of radiation therapy in the setting of concurrent chemotherapy, using three-dimensional conformal radiation therapy for non-small-cell lung cancer.

Methods and Materials: Eligibility included patients with histologically proven, unresectable Stages I to III non-small-cell lung cancer. Concurrent chemotherapy consisted of paclitaxel, 50 mg/m^2, and carboplatin, AUC of 2, given weekly. The radiation dose was to be sequentially intensified by increasing the daily fraction size, starting from 75.25 Gy/35 fractions.

Results: The Phase I portion of this study accrued 17 patients from 10 institutions and was closed in January 2004. After the initial 8 patients were accrued to cohort 1, the trial closed temporarily on September 26, 2002, due to reported toxicity. Two acute treatment-related dose-limiting toxicities (DLTs) were reported at the time: a case of grade 5 and grade 3 radiation pneumonitis. The protocol, therefore, was revised to de-escalate the radiation therapy dose (74 Gy/37 fractions). Patients in cohort 1 continued to develop toxicity, with 6/8 (75%) patients eventually developing grade ≥3 events. Cohort 2 accrued 9 patients. There was one DLT, a grade 3 esophagitis, in cohort 2 in the first 5 patients (1/5 patients) and no DLTs for the next 2 patients (0/2 patients).

Conclusions: The maximum tolerated dose was determined to be 74 Gy/37 fractions (2.0 Gy per fraction) using three-dimensional conformal radiation therapy with concurrent paclitaxel and carboplatin therapy. This dose level in the Phase II portion has been well tolerated, with low rates of acute and late lung toxicities. **© 2010 Elsevier Inc.**

Lung cancer, RTOG, Concurrent chemoradiation therapy, Dose escalation.

INTRODUCTION

The standard dose, volume, and beam arrangements for the treatment of non-small-cell lung cancer (NSCLC) were established by Radiation Therapy Oncology Group (RTOG) dose escalation trial 7301 (1). This trial included patients with inoperable stage III disease, who received radiation therapy only. Since current radiation parameters were established by that trial, a number of changes in treatment have occurred, including the addition of concurrent chemotherapy and the application of three-dimensional conformal radiation therapy (3DCRT). RTOG 9311 was a subsequent protocol that escalated the radiation dose with 3DCRT without concurrent chemotherapy (2). The total dose was based on the percent volume of normal lung exceeding 20 Gy (V20). RTOG 9311 established that the maximum tolerated doses (MTD) of radiation alone were 83.8 Gy for patients with V20 values of <25% and 77.4 Gy for V20 values between 25 and 36%. Near the close of this study, results of randomized trials were reported that demonstrated a survival advantage in favor of concurrent chemotherapy compared to radiation alone or to sequential chemotherapy followed by radiation therapy (3–7). Therefore, the objectives for RTOG 0117 were to establish the MTD of radiation therapy in the setting of concurrent paclitaxel and carboplatin therapy, using 3DCRT for patients with inoperable NSCLC (Phase I), and to estimate the percentage of patients who survive at least 12 months with this regimen (Phase II). This report addresses the Phase I results of this trial.

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METHODS AND MATERIALS

Between July 13, 2001, and January 13, 2004, 17 patients were enrolled in the Phase I portion of the study. Eligible patients had histologically proven stage I to IIIB NSCLC, Zubrod performance status levels of 0 to 1, a weight loss of ≤5% within the previous 6 months, a forced expiratory volume at 1 second of ≤1 liter, and atelectasis involvement, if present, in less than one lung. Based on conformal treatment planning, the volume of the lung at or exceeding 20 Gy (V20) had to be ≤30% and a mean esophagus dose of ≤34 Gy and a volume of esophagus exceeding 55 Gy (V55) of ≤30%. Exclusion criteria included prior radiation therapy to the thorax, prior chemotherapy or biologic cancer therapy for lung cancer within the past 2 years, prior or concurrent malignancy (except non-melanoma skin cancer), unless disease free for 1 year or more, supraclavicular lymph node metastasis, pleural or pericardial effusions, and superior vena cava syndrome. The metastatic workup included pulmonary function testing, chest x ray, computed tomography (CT) scans of the chest and upper abdomen, either magnetic resonance or CT imaging of the brain, a bone scan, complete blood counts, and electrolyte, alkaline phosphatase, and liver function tests. Positron emission tomography (PET) was not required as it was not routine at the outset of the study, although 7 of 17 (41%) patients were staged with a diagnostic ^{18}F-fluorodeoxyglucose-PET scan.

Treatment consisted of fractionated radiation therapy given with concurrent weekly chemotherapy consisting of paclitaxel, 50 mg/m^2, administered over 1 hour on days 1, 8, 15, 22, 29, 36, and 43, followed by carboplatin, AUC of 2, administered over 30 minutes on days 1, 8, 15, 22, 29, 36, and 43. Adjuvant systemic chemotherapy was optional following completion of radiation therapy, although no patients received it.

Radiation therapy was initially planned to be given by a dose escalation design using increasing doses per fraction (75.25 Gy at 2.15 Gy per fraction, 80.5 Gy at 2.3 Gy per fraction, 79.5 Gy at 2.65 Gy per fraction, and 75 Gy at 3 Gy per fraction) (Table 1). However, due to excessive toxicity at dose level 1 (75.25 Gy at 2.15 Gy per fraction), an amendment was made to the protocol in January 2003, and the dosage for cohort 2 was de-escalated to 74 Gy at 2 Gy per fraction, and this dose was opened to patient accrual in February 2003 (Table 1). The trial was closed after accrual to Phase I was completed in January 2004 and reopened in August 2004 for Phase II accrual at the dose level of 74 Gy. 3DCRT was required. Radiation doses were prescribed to the isocenter, using water-based calculations. Gross tumor volume (GTV) was defined as the primary tumor and any lymph nodes exceeding 1 cm in greatest diameter. The GTV was expanded by 1 to 1.5 cm to achieve the planning target volume (PTV). No clinical target volume was specifically delineated. Elective nodal volumes were not included within the PTV. The protocol was designed to be stringent with respect to radiation dose to the normal lung and esophagus. Patients must have met a V20 of ≤30%, a mean esophagus dose of ≤34 Gy, and an esophageal V55 of ≤30%. V20 was calculated by using total lung minus the PTV as the normal lung volume. The radiation treatment plan for each patient was stored centrally at the image-guided therapy center and scored for compliance by the principal investigator.

Statistical design and analysis

The aim of the Phase I portion of this study was to establish the MTD of radiotherapy (RT) that could be delivered using 3DCRT concurrently with paclitaxel and carboplatin chemotherapy. Seven patients were required per dose arm to evaluate for acute dose-limiting toxicities (DLTs). Toxicity was monitored continuously as each patient was accrued, and each patient was evaluated for acute DLT during the first 90 days from the start of RT. Acute RT and chemotherapy toxicities were graded using Common Toxicity Criteria version 2.0 (8). Late RT toxicities were reported using RTOG/EORTC late toxicity criteria (9). Protocol-specified DLTs were defined as acute grade 3 or 4 treatment-related nonhematologic toxicities (excluding nausea, vomiting, and alopecia), acute grade 4 treatment-related hematologic toxicities, and grade 5 toxicity at any time.

Table 1. Dose escalation and de-escalation

Dose level	Radiation Therapy: Original Protocol	Radiation Therapy: Amended Protocol	Cohort
1	75.25 Gy / 35 fxs (2.15 Gy per fraction)		1
2	80.5 Gy / 35 fxs (2.3 Gy per fx) (escalation dose)†	74 Gy / 37 fxs (2.0 Gy per fx) (de-escalation dose)	2 (MTD)
3	79.5 Gy / 30 fxs (2.65 Gy per fx) (escalation dose)†	70 Gy / 35 fxs (2.0 Gy per fx) (de-escalation dose)‡	
4	75 Gy / 25 fxs (3.0 Gy per fx) (escalation dose)†	N/A	

Abbreviations: fx = fractions; N/A = not applicable.
† Amended since dose level 1 was too toxic.
‡ Unnecessary since dose level 2 was deemed safe.

One dose level was opened for patient accrual at a time. Dose escalation proceeded, and the current dose was considered acceptable if, after 90 days of evaluation, no DLTs were observed in the first 5 patients (0/5). If there was one acute DLT observed in the first 5 evaluable patients (1/5) and no acute DLTs were observed in the next two evaluable patients (0/2), then the dose level was deemed safe. At a given dose level, this design gives at least 90% confidence that the true acute DLT rate at a given dose level is less than 40% and that for any given dose level, the probability of not escalating when the true toxicity rate is 40% or higher is at least 83%.

Frequency tables with counts and percentages were used to describe pretreatment characteristics and toxicities for each cohort. Results for all eligible patients are reported. The assessment of DLTs was based only on the first 7 evaluable patients per arm.

RESULTS

Accrual for the Phase I portion was from nine RTOG institutions (15 of 17 patients) and one RTOG community clinical oncology program.

The Phase I portion of this study had 8 eligible and evaluable patients in cohort 1 (receiving 75.25 Gy/35 fractions) and 9 patients in cohort 2 (receiving 74 Gy/37 fractions). The distributions of pretreatment characteristics for each of the Phase I arms are given in Table 2. Patients ranged in age from 48 to 81 years old. Cohort 1 had 4 (50%) patients with a Zubrod performance status of 1 compared to cohort 2, which had 3 (33%) Zubrod status 1 patients. All patients in cohort 2 were stage IIIA, while cohort 1 had a single stage IB patient, and the rest had stage IIIA or IIIB. The majority of