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A Phase I/II Radiation Dose Escalation Study with Concurrent Chemotherapy for Patients with Inoperable Stages I-III Non-Small Cell Lung Cancer: The Phase I Results of RTOG 0117

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Abstract

Background—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 (MTD) of radiation therapy, in the setting of concurrent chemotherapy, using 3DCRT for NSCLC.

Methods—Eligibility included patients with histologically proven, unresectable Stages I-III NSCLC. Concurrent chemotherapy consisted of paclitaxel 50 mg/m2 and carboplatin AUC=2 given weekly. 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 eight patients were accrued to Cohort 1, the trial closed temporarily on September 26, 2002 due to reported toxicity. Two acute treatment-related DLTs were reported at the time: a grade 5 and a grade 3 radiation pneumonitis. The protocol, therefore, was revised to de-escalate the RT dose (74 Gy/37 fractions). Patients in Cohort 1 continued to develop toxicity with 6/8 (75%) 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) and no DLTs for the next 2 patients (0/2).

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Conclusions—The MTD was determined to be 74 Gy/37 fractions (2.0 Gy per fraction) using 3DCRT with concurrent paclitaxel and carboplatin. This dose level, in the Phase II portion, has been well tolerated with low rates of acute and late lung toxicities.

Keywords

lung cancer; RTOG; concurrent chemoradiation therapy; dose escalation

Background

The standard dose, volume and beam arrangements for the treatment of non-small cell lung cancer (NSCLC) were established by the Radiation Therapy Oncology Group (RTOG) dose-escalation trial 7301.1 This trial included patients with inoperable Stage III disease who received radiation therapy alone. Since the 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 radiation dose using 3DCRT without concurrent chemotherapy.2 The total dose was based on the percent volume of normal lung exceeding 20 Gy (V20). RTOG 9311 established the maximum tolerated dose (MTD) of radiation alone to be 83.8 Gy for patients with V20 values of <25% and 77.4 Gy for V20 values between 25-36%. Near the closure of this study, the results of randomized trials were reported that demonstrated a survival advantage in favor of concurrent chemotherapy compared to radiation alone or 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 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.

Materials and Methods

Between July 13, 2001 and January 13, 2004, 17 patients were enrolled to the Phase I portion of the study. Eligible patients had histologically-proven stages I-IIIB NSCLC, Zubrod performance status 0-1, ≤ 5% weight loss within the past 6 months, a forced expiratory volume at 1 second of ≥ 1 liter, and atelectasis, if present, must be less than one lung. Based on conformal treatment planning, the volume of lung at or exceeding 20 Gy (V20) must have been ≤ 30%, the mean esophagus dose ≤ 34 Gy, and the volume of esophagus exceeding 55Gy (V55) ≤ 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 one or more years, 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) of the chest and upper abdomen, either magnetic resonance imaging or CT of the brain, a bone scan, complete blood counts, electrolytes, alkaline phosphatase, and liver function tests. Positron emission tomography was not required as it was not routine at the outset of the study, though 7 out of 17 (41%) patients were staged with a diagnostic FDG-PET scan.

Treatment consisted of fractionated radiation therapy given with concurrent weekly chemotherapy consisting of paclitaxel 50 mg/m2 over 1 hour on days 1, 8, 15, 22, 29, 36, and 43 followed by carboplatin AUC=2 over 30 minutes days 1, 8, 15, 22, 29, 36, and 43. Adjuvant systemic chemotherapy was optional following completion of radiation therapy, though 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 75Gy 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 Cohort 2 was de-escalated to 74 Gy at 2 Gy per fraction and this dose opened to 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 74 Gy dose level. Three-dimensional conformal radiation therapy 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 (CTV) 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 V20 ≤ 30%, mean esophagus dose ≤ 34 Gy, and esophageal V55 ≤ 30%. V20 was calculated by using total lung minus PTV as the normal lung volume. The radiation treatment plan for each patient was stored centrally at the Image-Guided Therapy Center (ITC) 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 maximum tolerated dose (MTD) of radiotherapy (RT) that can be delivered using three-dimensional conformal radiation treatment (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 the Common Toxicity Criteria version 2.0 (CTC v 2.0)8. Late RT toxicities were reported using the RTOG/EORTC Late Toxicity Criteria9. The protocol-specified DLTs were defined as follows: acute grade 3 or 4 treatment-related non-hematologic toxicities (excluding nausea, vomiting, and alopecia), acute grade 4 treatment-related hematologic toxicities, and grade 5 toxicity at any time.

One dose level was open for 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 observed in the next two evaluable patients (0/2), then the dose level was deemed to be 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 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 9 RTOG institutions (15 out of 17 patients) and 1 RTOG CCOP.

The Phase I portion of this study had 8 eligible and evaluable patients in Cohort 1 (75.25 Gy/35 fractions) and 9 in Cohort 2 (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%) patients. All patients in Cohort 2 were stage IIIA

while Cohort 1 had a single stage IB patient, with the rest having Stage IIIA or IIIB. The majority of patients on the Phase I portion were white, not of Hispanic origin (76%).

Table 3 shows the chemotherapy and acute RT toxicities. Table 4 lists the specific grade ≥ 3 non-hematologic toxicities and the specific grade ≥ 4 hematologic toxicities. There were 6 (75%) patients on Cohort 1 that reported a grade ≥ 3 non-hematologic toxicity and no patients reported a grade ≥ 4 hematologic toxicity. One patient (13%) in Cohort 1 reported a grade 4 pain toxicity (Case D, myalgia/back pain) and 1 patient reported a grade 5 toxicity (Case A, Infection/febrile neutropenia-infection NOS). The patient with the grade 5 toxicity had developed a radiation pneumonitis a few months following therapy and was treated with oral prednisone. This patient had a prolonged hospitalization and ultimately died of a systemic fungal infection that may have been related to the administration of steroids. A data safety and monitoring committee, within the RTOG, met to review this patient's medical record and decide whether or not the event was related to treatment and the decision of the committee was to count this event as treatment-related and, therefore, a DLT. Besides this DLT, there was another patient who experienced a DLT in a grade 3 pneumonitis (Case E). Since there was 1 DLT in the first 5 patients (1/5) and 1 DLT in the next two patients (1/2), this dose level (75.25 Gy/35 fx at 2.15 Gy per fx) was determined to be too toxic and dose escalation was impossible from this starting dose. Therefore, the protocol was amended to include an arm that de-escalated the radiation therapy dose to 74 Gy in 2 Gy daily fractions (Arm 2). Arm 2 had 6 (67%) patients who reported a grade ≥ 3 non-hematologic toxicity and no patients who reported a grade ≥ 4 hematologic toxicity. There was 1 (11%) grade 4 toxicity reported in Cohort 2, scored as 'hypersensitivity, not otherwise specified'. This toxicity as well as the other toxicities reported in Cohort 2, except for a grade 3 esophagitis (Case J), was determined by study chair and Deputy Group Chair review to be unrelated to treatment and not DLTs. Therefore, since there was one DLT in Cohort 2 in the first 5 patients (1/5) and no DLTs for the next 2 patients (0/2), the MTD was determined to be 74 Gy/37 fx (2.0 Gy per fraction) and dose de-escalation was not necessary.

Late radiotherapy toxicities are shown in Table 5. Two patients in Cohort 1 experienced grade 3 pulmonary events, scored as pneumonitis and hypoxemia, respectively. Two patients in Cohort 2 experienced grade 3 events, one with esophagitis and one with pulmonary fibrosis. Overall, the pulmonary toxicity in Cohort 1 was greater than expected, with 6 of 8 patients experiencing either pneumonitis (4/8) (including patient with the grade 5 infection), hypoxemia (1/8), or pulmonary fibrosis (1/8).

The radiation therapy treatment plans were submitted by the enrolling institutions and then reviewed by the principal investigator with respect to protocol compliance for GTV, PTV and normal tissue volumes. Overall, 14 of the 17 digitally submitted plans were reviewable. Three plans could not be reviewed due to failed digital data integrity. Of the 14 reviewed datasets, contoured structures were per protocol or within acceptable variation in 13 (93%) (Table 6).

The Phase II portion of the study was initiated using 74 Gy as the target dose. The Phase II portion has recently completed accrual and has continued to show low rates of acute and late lung toxicities at this dose level. These results will be reported when the follow-up period can adequately assess the 12-month survival rate: the Phase II primary endpoint.

Discussion

The currently accepted "standard of care" for patients with locally-advanced NSCLC is concurrent radiation plus chemotherapy. In recent years, most research has focused on which chemotherapy drugs to use and how to integrate them with radiation therapy. Moreover, little attention has been given to optimizing the radiation therapy. In particular, the nationally

accepted standard radiation prescription dose has remained at the same level (60-63 Gy) for more than 30 years.[1] Doses in this range provide inadequate local control. The 5 year local control rate on the concurrent QD arm of RTOG 9410, delivering a dose of 63 Gy in 1.8 Gy daily fractions, was 65.4%.10 Results from studies of stereotactic radiation therapy for lung cancer estimate that biological equivalent doses of 100 Gy are needed to achieve local control for the small volume Stage I lung cancers treated with that technique11. Unfortunately, there are no prospective data to show what radiation doses mediastinal and pulmonary structures will tolerate using concurrent chemotherapy with conventionally fractionated radiation therapy. Prospective studies are underway to determine whether radiation dose escalation improves local control and survival in Stage III lung cancer.

There have been many advances since RTOG 73-01 established 60 Gy as the standard of care. These include CT-based treatment planning, conformal radiation therapy, positron emission tomography (PET), and knowledge of tumor motion during radiation delivery. These technological advances, along with knowledge that tumor failures in elective nodal regions are ≤ 10%, enabled the delivery of higher doses of radiation therapy to reduced target volumes covering known tumor. RTOG 9311 employed 3DCRT to safely escalate fractionated radiation dose to 83.8 Gy in patients who did not receive concurrent chemotherapy.[2]

RTOG 0117 was designed as a Phase I/II study with two objectives; to determine the MTD of radiation therapy in the setting of concurrent chemotherapy and to determine the 12-month survival rate at that MTD. This report covers the first objective.

Our trial was initiated with a dose of 75.25 Gy in 2.15 Gy daily fractions (roughly 10% lower than the MTD for 9311) because of concern about the additive toxicity of concurrent chemotherapy. It turns out that our starting dose was too ambitious; 6/8 (75%) of patients experienced grade 3-5 non-hematological toxicity. The total dose was then reduced to 74 Gy in 2 Gy daily fractions. There was 1 DLT in the first 5 patients treated to 74 Gy and 0 in the next two patients so the MTD was determined to be 74 Gy/37 fractions (2 Gy per fraction). There was no difference between the tumor volumes, V20, and mean lung dose for patients on Arms 1 and 2. On the Phase II portion, 74 Gy has been well-tolerated.

Since the completion of RTOG 0117, two other groups have reported toxicity results of 74 Gy with weekly carboplatin and paclitaxel. The NCCTG reported Phase I results of a radiation dose escalation study with concurrent chemotherapy (NCCTG 0028).[12] The study accrued 13 patients, who received concurrent weekly carboplatin (AUC = 2) and paclitaxel (50 mg/m^2) and 3DCRT radiotherapy with no elective nodal radiation. Dose escalation began at a level of 70 Gy and was escalated in 4 Gy increments to determine the MTD. No dose-limiting toxicities (DLTs) were reported for the three patients who received 70 Gy. One DLT occurred in the six patients treated to 74 Gy. Two DLTs occurred in the four patients treated to 78 Gy. There were a total of 3 DLTs observed, grade 3 pneumonitis (n= 2) and 1 grade 4 pneumonitis. Similar to the findings of RTOG 0117, the MTD of N0028 was determined to be 74 Gy. With a median follow-up of 28 months, the median survival time was 37 months. The CALGB recently reported preliminary results of a 2-arm Phase II trial (CALGB 30105) treating Stage III patients with chemoradiotherapy with both arms using 74 Gy.[13] Patients received either induction carboplatin (AUC 6) and paclitaxel (225 mg/m$^{2)}$ followed by concurrent weekly carboplatin (AUC 2) and paclitaxel (45 mg/m^2) during radiation versus induction carboplatin (AUC 5) and gemcitabine (1000 mg/m^2) followed by concurrent gemcitabine twice weekly (35 mg/m^2) during radiation. The trial enrolled 69 patients and was reported with a median follow up of 16.4 months. Median survival times were 24.2 months for the carboplatin/paclitaxel arm and 17 months for the carboplatin/gemcitabine arm. The median progression-free survival was 15.2 months. The gemcitabine arm was closed early due to 13% grade 5 pulmonary events. Prospective data evaluating toxicity with the use of chemotherapy agents other than carboplatin

and paclitaxel or carboplatin and gemcitibine concurrently with radiation doses of 70 Gy or higher are lacking. As such, the use of weekly doses of carboplatin and paclitaxel has carried over into the Phase III trial evaluating the value of high-dose radiation therapy.

Conclusions

Based on the results of RTOG 0117, NCCTG N0028, and CALGB 30105, 74 Gy has been established as the MTD of radiation therapy when given with weekly concurrent carboplatin and paclitaxel. These three cooperative groups have initiated a Phase III Intergroup trial (RTOG 0617/ NCCTG N0628/ CALGB 30609) testing 74 Gy versus 60 Gy with concurrent chemotherapy for patients with inoperable Stage III NSCLC.

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Table 1

Dose Escalation/De-escalation

Dose Level	Radiation Therapy		
	Original Protocol	Amended Protocol	
1	75.25 Gy / 35 fxs (2.15 Gy per fraction)		Cohort 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)	Cohort 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	

† Amended since dose level 1 was too toxic.

‡ Unnecessary since dose level 2 was deemed safe.

Table 2

Pretreatment Characteristics

	Arm 1: 75.25 Gy/35 fx (n=8)		Arm 2: 74 Gy/37 fx (n=9)	
Age				
Median	65.5		68	
Range	48-77		52-81	
	n	%	n	%
Gender				
Male	7	88	8	89
Female	1	13	1	11
Race				
White, not of Hispanic origin	7	88	6	67
Hispanic or Latino	0	0	2	22
Black, not of Hispanic origin	1	13	1	11
Zubrod Performance Status				
0	4	50	6	67
1	4	50	3	33
Stage				
IB	1	13	0	0
IIA	0	0	0	0
IIB	0	0	0	0
IIIA	3	38	9	100
IIIB	4	50	0	0
Histology				
Squamous	3	38	2	22
Adenocarcinoma	4	50	3	33
Large Cell	1	13	1	11
Carcinoma NOS	0	0	3	33
Location of Primary				
Right upper lobe	5	63	3	33
Right middle lobe	0	0	1	11
Right lower lobe	0	0	2	22
Left upper lobe excluding lingual	3	38	1	11
Left lower lobe	0	0	1	11
Other (right hilar)	0	0	1	11

Table 3

Chemotherapy and Acute Radiotherapy Toxicity

	Arm 1: 75.25 Gy/35 fx (n=8)					Arm 2: 74 Gy/37 fx (n=9)				
	Grade					Grade				
Category	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Allergy/immunology	0	0	1	0	0	0	0	0	1	0
Blood/bone marrow	0	2	4	0	0	3	0	5	0	0
Cardiovascular (arrhythmia)	0	0	1	0	0	0	1	0	0	0
Cardiovascular (general)	0	0	1	0	0	0	1	2	0	0
Coagulation	0	0	1	0	0	0	0	1	0	0
Constitutional symptoms	0	2	0	0	0	1	3	1	0	0
Dermatology/skin	2	1	0	0	0	4	1	0	0	0
Gastrointestinal	2	2	1	0	0	2	3	2	0	0
Hemorrhage	1	0	0	0	0	1	0	0	0	0
Hepatic	1	2	0	0	0	0	0	0	0	0
Infection/febrile neutropenia	0	1	0	0	1	0	0	1	0	0
Metabolic/laboratory	1	2	1	0	0	1	0	0	0	0
Musculoskeletal	0	1	1	0	0	0	1	0	0	0
Neurology	0	1	1	0	0	0	1	3	0	0
Pain	0	2	0	1	0	1	0	2	0	0
Pulmonary	0	1	3	0	0	1	2	1	0	0
Renal/genitourinary	0	0	0	0	0	0	1	0	0	0
Worst non-hematologic	1 (13%)	1 (13%)	4 (50%)	1 (13%)	1 (13%)	0 (0%)	3 (33%)	5 (56%)	1 (11%)	0 (0%)
Worst overall	1 (13%)	1 (13%)	4 (50%)	1 (13%)	1 (13%)	0 (0%)	1 (11%)	7 (78%)	1 (11%)	0 (0%)

Table 4

Non-Hematogic Grade ≥ 3 Toxicities and Hematogic Grade ≥ 4 Toxicities from Table 2

RX	Case*	Category	Toxicity	Grade
Arm 1	A	Allergy/immunology	Hypersensitivity NOS	3
		Infection/febrile neutropenia	**Infection NOS (DLT)**	**5**
		Pulmonary	Dyspnea NOS	3
			Pneumonitis NOS	3
	B	Cardiovascular (general)	Cardiac troponin I increased	3
		Coagulation	Prothrombin time prolonged	3
		Metabolic/laboratory	Hyperglycemia NOS	3
	C	Gastrointestinal	Dehydration	3
	D	Cardiovascular (arrhythmia)	Sinus tachycardia	3
		Musculoskeletal	Muscle weakness NOS	3
		Pain	Pain-other: back pain	4
			Myalgia	3
		Pulmonary	Pleural effusion	3
	E	**Pulmonary**	**Pneumonitis NOS (DLT)**	**3**
	F	Neurology	Convulsions NOS	3
Arm 2	G	Cardiovascular (general)	Hypotension NOS	3
		Constitutional symptoms	Weight decreased	3
		Gastrointestinal	Anorexia	3
			Dehydration	3
		Neurology	Depression NEC	3
	H	Allergy/immunology	Hypersensitivity NOS	4
	I	Cardiovascular (general)	Thrombosis NOS	3
	J	**Gastrointestinal**	Nausea	3
			Esophagitis NOS (DLT)	**3**
			Dehydration	3
			Esophageal spasm	3
			Vomiting NOS	3
		Infection/febrile neutropenia	Infection with grade 3 or 4 neutropenia	3
		Neurology	Tremor NEC	3
	K	Coagulation	Prothrombin time prolonged	3
		Neurology	Syncope	3
		Pain	Chest pain	3
		Pulmonary	Dyspnea NOS	3
			Pneumonitis NOS	3
			Hypoxia	3

RX	Case*	Category	Toxicity	Grade
	L	Pain	Bone pain	3

*The case numbers of the 12 out of 17 possible patients (listed above) were changed to letters to protect their privacy.

Table 5

Late Radiotherapy Toxicity

	Arm 1: 75.25 Gy/35 fx (n=7)			Arm 2: 74 Gy/37 fx (n=8)		
	Grade			Grade		
	1	2	3	1	2	3
Esophagus	3	1	0	2	0	1
Skin (within the irradiated field)	1	0	0	2	0	0
Lung	3	2	1	1	2	1
Heart	1	0	0	0	0	0
Subcutaneous tissue	1	0	0	1	0	0
Spinal cord	1	0	0	0	0	0
Bone	1	0	0	0	0	0
Other	0	1	1	1	1	0
Worst overall	2 (29%)	2 (29%)	2 (29%)	2 (25%)	2 (25%)	2 (25%)

Table 6

Radiotherapy Review (n=17)

Not Reviewed* 3 (18%)			
Reviewed 14 (82%)			
	Organs at Risk Score		
Tumor Volume Score	**Per Protocol**	**Acceptable Variation**	**Total**
Per Protocol	8 (57%)	3 (21%)	11 (79%)
Acceptable Variation	1 (7%)	1 (7%)	2 (14%)
Unacceptable Variation	1 (7%)	0 (0%)	1 (7%)
Total	10 (71%)	4 (29%)	14 (100%)

* Failed digital data integrity