Induction Chemotherapy with Carboplatin, Irinotecan, and Paclitaxel Followed by High Dose Three-Dimension Conformal Thoracic Radiotherapy (74 Gy) with Concurrent Carboplatin, Paclitaxel, and Gefitinib in Unresectable Stage IIIA and Stage IIIB Non-small Cell Lung Cancer

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Introduction: Combined modality therapy is a standard therapy for patients with unresectable stage III non-small cell lung cancer (NSCLC). Gefitinib is active in advanced NSCLC, and in preclinical models, it potentiates the activity of radiation therapy. We investigate the tolerability of gefitinib in combined modality therapy in combination with three-dimensional thoracic conformal radiation therapy (3-dimensional TCRT).

Methods: Stage III patients with a good performance status were treated with induction chemotherapy (carboplatin area under the curve [AUC] of 5, irinotecan 100 mg/m^2, and paclitaxel 175 mg/m^2 days 1 and 22) with pegfilgrastim support followed by concurrent chemotherapy (carboplatin AUC 2, and paclitaxel 45 mg/m^2 weekly) and gefitinib 250 mg daily beginning on day 43 with 3-dimensional TCRT to 74 Gy.

Results: Between March 2004 and January 2006, 23 patients received treatment on the trial: median age 62 years (range 44–82), 52% female, 61% stage IIIA, 61% performance status 0, 17% ≥5% weight loss, and 91% underwent positron emission tomography staging. Induction chemotherapy with pegfilgrastim support was well tolerated and active (partial response rate, 24%; stable disease, 76%; and early progression, 0%). Twenty-one patients initiated the concurrent chemoradiation, and 20 patients completed therapy to 74 Gy. The primary toxicities of concurrent chemoradiation were grade 3 esophagitis (19.5%) and cardiac arrhythmia (atrial fibrillation) (9.5%). The median progression-free survival and overall survival were 9 months (95% confidence intervals [CI]: 7–13 months) and 16 months (95% CI: 10–20 months), respectively.

Conclusions: Treatment with induction chemotherapy and gefitinib concurrent with 3-dimensional TCRT has an acceptable toxicity and tolerability, but the survival results were disappointing.

Key Words: High-dose radiation, Combined modality therapy, Conformal radiation therapy, Epidermal growth factor receptor, Tyrosine kinase inhibitor, Concurrent chemoradiotherapy.

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Lung cancer is the leading cause of cancer-related deaths in the United States, and in 2007 it is estimated that more people died from lung cancer than prostate, colorectal, and breast cancer combined.[1] Eighty-five percent of the cases of lung cancer are non-small cell lung cancer histology (NSCLC), and 30 to 45% will be stage IIIA or B at the time of diagnosis, and are considered potentially curable.[2,3] In the United States, the standard of care for patients with a good performance status is the combination of systemic dose chemotherapy and thoracic radiation therapy, often referred to as combined modality therapy.[4] Unfortunately, the majority of patients treated with combined modality therapy experience locoregional or distant (or both) progression of their disease. We have previously reported a phase I/II dose escalation incorporating 3-dimensional thoracic conformal radiation therapy (3-dimensional TCRT) into the treatment paradigm of induction and concurrent carboplatin and paclitaxel.[5] In this trial, we successfully escalated the dose of 3-dimensional TCRT from 60 to 74 Gy in 62 patients with unresectable stage III NSCLC with an acceptable rate of acute and late toxicities. The primary acute toxicity was esophagitis, but only 8% of patients experienced grade 3 or 4 esophagitis. The overall survival observed on this trial was encouraging, and the median survival time was 25 months, and the 1-, 3-, 5-year survival rates with 95% confidence intervals (CI) were 71% (60–80%), 39% (27%–51%), and 26% (15%–38%),

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respectively.[6] Despite the more aggressive locoregional treatment, at least 35% of patients experienced locoregional failures. A separate analysis of prognostic factors of patients treated on our dose escalation trials revealed that the postinduction chemotherapy gross tumor volume (GTV) was predictive of survival.[7] This observation provided the rationale that a more aggressive induction chemotherapy treatment may reduce the intrathoracic tumor volume before initiating the chemoradiotherapy and improve locoregional control and survival. Our subsequent stage III trial was a phase I trial investigating further dose escalation of 3-dimensional TCRT.[8] On this trial, we incorporated induction chemotherapy with carboplatin, paclitaxel, and irinotecan (CIP) with growth colony stimulating factor for two cycles, which we had previously investigated in advanced disease.[9,10] The induction therapy with growth colony stimulating factor support was well tolerated, and the rate of all toxicities was less than 10%, and only 8% of cycles were complicated by grade 3 or 4 neutropenia.

At the time this trial was developed, gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), had revealed promising activity in phase II trials in patients with advanced NSCLC who had progressed after one or two therapies.[11,12] Two large phase III trials using carboplatin/paclitaxel and cisplatin/gemcitabine with and without gefitinib had been completed, but the survival results were not available.[9,10] Gefitinib appeared to be a promising agent for the treatment of advanced stage disease, and preclinical data indicated that the gefitinib may potentiate the activity of radiation therapy.[13–16] Given the safety and tolerability data from our previous trials, the combination of induction chemotherapy with CIP, and concurrent chemotherapy with weekly carboplatin and paclitaxel with 3-dimensional TCRT to 74 Gy appeared to be an appropriate treatment paradigm to investigate gefitinib in the treatment of unresectable stage III disease.

PATIENTS AND METHODS

Eligibility

Patients eligible for this trial were required to have a cytologic or histologic diagnosis of stage IIIA or IIIB disease and be deemed appropriate candidates for combined modality therapy. All patients were reviewed by a thoracic radiologist, pulmonologist, thoracic surgeon, radiation oncologist, and medical oncologist. Initial staging consisted of a chest radiograph and a staging chest computed tomography (CT) scan, which included full visualization of the liver and adrenal glands. Radionuclide bone scans and/or positron emission tomography (PET) scans were required as was either a CT or magnetic resonance imaging scan of the brain. Patients with supraclavicular adenopathy, superior sulcus tumors, or pleural effusion were excluded. Patients were required to have Eastern Cooperative Oncology Group performance status of 0 or 1 and could not have received prior chemotherapy or radiotherapy to the chest. Other required parameters were as follows: absolute neutrophil count (ANC) $\geq$1500/mm^3, platelet count $\geq$100,000/mm^3, serum creatinine $<$1.6 mg/dL or Cockcroft calculated creatinine clearance $>$40 mL/min, serum bilirubin $\leq$1.5 times upper limit of institutional normal, serum aspartate aminotransferase and alanine aminotransferase $\leq$2.5 times upper limit of institutional normal. Pulmonary function tests were required to document a forced expiratory volume 1 second of $>$800 mL. Subjects taking phenytoin, rifampin, barbiturates, carbamazepine, and St. John's Wort and patients with a prior malignancy who were disease free $<$5 years were excluded (except carcinoma in situ of the cervix or breast and nonmelanomatous skin cancer). Of note, there was not an inclusion or exclusion criteria related to weight loss. Patients underwent a bronchoscopy, mediastinoscopy, or transthoracic fine-needle aspiration for diagnosis and staging as clinically indicated. This trial was approved by the Protocol Review Committee of the Lineberger Comprehensive Cancer Center (LCCC) and the Institutional Review Board of the University of North Carolina School of Medicine and labeled LCCC 0215. All patients provided informed consent before enrollment on this trial.

Treatment Administration

Patients entered onto this trial received induction chemotherapy with carboplatin area under the concentration curve (AUC) of 5 by intravenous (IV) infusion using the Calvert Equation,[17] irinotecan 100 mg/m^2 IV infusion, and paclitaxel 175 mg/m^2 IV infusion, all given on day 1 and 22. Patients received pegfilgrastim 6 mg on the day 2 and 23 of induction chemotherapy. Details of this regimen have been published previously.[18,19] On day 43, patients received 7 or 8 weekly treatments of paclitaxel 45 mg/m^2/wk over 1 hour, carboplatin AUC 2, and gefitinib 250 mg orally daily with concurrent with TCRT. Treatment on days 22 and 43 required an ANC of at least 1500/mm^3 and platelets of at least 100,000/mm^3. A complete blood count was monitored weekly during concurrent chemoradiotherapy. The carboplatin dose was reduced to an AUC of 1 if the ANC was $<$1000/mm^3 but greater than 500/mm^3 or the platelets were $<$75,000/mm^3. Both paclitaxel and carboplatin were held if the ANC was $<$500/mm^3 or the platelets were $<$50,000/mm^3. In the initial protocol, patients continued to receive gefitinib 250 mg daily for 2 years or until disease progression or unacceptable toxicity. The trial was amended after an interim analysis of Southwest Oncology Group (SWOG) trial 0023 by Data and Safety Committee of the SWOG revealed that the addition of gefitinib after completion of chemoradiotherapy in stage III disease did not improve survival.[20] The gefitinib was discontinued after completion of TCRT, but was continued during the TCRT.

TCRT was initiated on day 43 concurrent with weekly paclitaxel, carboplatin, and gefitinib as noted above. Patients underwent a planning CT after the second cycle of chemotherapy. The initial clinical target volume (CTV_I) was defined as the prechemotherapy primary tumor volume, clinically positive lymph nodes and the bilateral (elective) mediastinum. Clinically positive lymph nodes were defined as nodes $\geq$1 cm in greatest diameter visualized on CT scan, mediastinoscopy-positive or lymph nodes that were $<$1 cm and positive on PET scan were included in the CTV_1. The PET scan was not used in the target volume delineation. The elective mediastinum was defined as the mediastinum 0.5 to 2.0 cm below the clavicular heads to 1.0 to 2.0 cm below the

carina or lowest clinically positive lymph nodes. The boost clinical target volume (CTV_B) was defined as the postinduction chemotherapy primary tumor and clinically positive lymph node regions involved initially. The initial treatment to the CTV_I was performed using AP/PA (anteroposterior/posteroanterior) fields. The CTV_I received a dose of 44 Gy with a 1.0 to 2.0 cm margin to account for subject motion, registration inaccuracies, set-up variation, and dose build-up. The total dose delivered to the CTV_I was determined by a spinal cord tolerance of 4750 cGy maximum. The boost treatment was accomplished with oblique fields off cord with a minimum of two beams. The off-cord boost received doses of 74 Gy to the CTV_B with a 1.0 to 2.0 cm margin. Patients received 2 Gy/d Monday through Friday with the exception of holidays with ≥6 MV photons. Dose limits for normal tissue were as follows: no more than 35% of the lung volume could receive >20 Gy (V_{20}), no part of the spinal cord could receive >50 Gy, and no part of the brachial plexus could receive >66 Gy. The V_{20} was calculated using the total lung volume defined as total lung minus the GTV. There were no required dose limits on the treatment for the heart and the esophagus; however, it was recommended that the entire heart (and/or left ventricle) not receive >60 Gy, and the full circumference of the esophagus not receive >60 Gy for 6 cm. Heterogeneity corrections were required in the treatment planning. Patients did not receive intensity modulate radiotherapy on this trial.

Response and Toxicity Evaluation

The response rate after two cycles of induction CIP was assessed during week 6 of treatment with a staging chest CT scan. All patients had a CT scan performed 2 months after the last dose of TCRT were followed clinically every 2 months with chest radiographs for the first 2 years. If patients had signs on physical examination (eg, palpable lymphadenopathy) or symptoms concerning for disease progression patients underwent the additional testing including repeat CT scans of the chest/abdomen, imaging of the brain, and bone scans as clinically indicated. The date of progression was defined as the date there was evidence of progression of disease on physical examination or radiographic imaging. Responses were assessed by standard World Health Organization criteria.[21] Toxicity was assessed using the Common Toxicity Criteria scale version 2.0. The primary dose-limiting toxicity was defined as grade 4 esophagitis.

Study Design and Statistical Design

The primary objective was to assess the toxicity and tolerability of the combination of induction CIP with pegfilgrastim supportive therapy, followed by concurrent carboplatin, paclitaxel, and gefitinib with high dose 3-dimensional TCRT in unresectable stage IIIA or B NSCLC. The secondary objectives were to estimate the overall and progression-free survival. It was anticipated that esophagitis would be the primary dose limiting toxicity (DLT), and the study was designed to stop if the rate of grade 4 esophagitis was statistically shown to be ≥10% at $\alpha = 0.091$. Accrual and continuous stopping rules were based on the primary DLT, grade 4 esophagitis, and were as follows: 2 primary DLTs in the first 3 subjects, 3 primary DLTs in the first 8 subjects, 4 primary DLTs in the first 14 patients, and 5 primary DLTs in the entire cohort ($n = 20$). Assuming a 20 to 30% nonevaluable rate, 24 to 26 patients were required. In addition to the stopping rules related to the primary DLT, there was an additional stopping rule related to the failure to complete protocol therapy: If >50% of patients who initiate treatment had treatment delays of >2 weeks or did not complete treatment due to toxicity, the trial would be stopped and reviewed. Other grade 4 nonhematologic toxicities were evaluated during and for up to 90 days after initiation the concurrent chemoradiotherapy, and were used to monitor for excessive toxicity. The Kaplan-Meier (or product limit) method was used to estimate the time to event functions of progression-free survival and overall survival. Progression-free survival has been defined as the time between the date of the start of treatment to disease progression or death (which ever occurs first) or the date of last contact. Overall survival has been defined as the time from the date of the start of treatment to the date of death or the date of last contact. Exact 95% confidence intervals were calculated for reported proportions (or percentages) of interest. Statistical analyses were performed with SAS statistical software, Versions 9.1, SAS Institute Inc., Cary, NC. An analysis of molecular studies will be provided in a separate article.

RESULTS

Patient Characteristics

Between March 2004 and January 2006, 24 patients were enrolled on the trial, and one withdrew informed consent before initiating therapy. Twenty-three received treatment on the trial, and the demographic data are presented on

TABLE 1. Patient Demographics

Characteristic	No. of Patients
Total no. of patients	23
Age (yr), median (range)	62 (44–82 yr)
Gender (male:female)	11:12
Race (white:African American)	19:4
Stage (IIIA:IIIB)	14:9
Weight loss (≥5%:<5%)	4:19
PS (0:1)	14:9
Histology (%)	
Adenocarcinoma	12 (52%)
Squamous	10 (44%)
Large cell carcinoma	1 (4%)
Pulmonary function tests, median (range)	
FEV_1, l (range)	1.9 (0.86–3.79)
FVC, l (range)	2.78 (1.87–5.53)
DLCO (range) (mL/min/mm Hg)[a]	15.8 (2.17–32.7)
Smoking history (%)	
Current smoker	8 (35%)
Former smoker	13 (56%)
Never smoker	2 (9%)
Positron emission scan staging	21 (91%)

[a] Data missing on one patient ($n = 22$).

Table 1. The median age was 62 years (range, 44–82). Twelve of the patients (52%) were female, and 14 (61%) were stage IIIA. Four patients (17%) had ≥5% weight loss, and 21 patients (91%) underwent PET scan staging. The majority of patients were former or current smokers (91%). One patient experienced a grade 4 hypersensitivity reaction related to paclitaxel and did not continue treatment on the trial, and one patient received one cycle of induction therapy on the trial and was subsequently found to be ineligible; 21 patients started and were considered evaluable for assessing the tolerability and toxicity of concurrent chemoradiotherapy in combination with gefitinib.

Induction Chemotherapy

Twenty-three patients received at least one treatment of CIP induction chemotherapy, and 43 cycles were given. The hematologic and nonhematologic toxicities are shown in Table 2. In general, the hematologic toxicities with induction CIP with pegfilgrastim supportive therapy were mild and acceptable. Only 2% of cycles were complicated by grade 3 or 4 neutropenia. The primary grade 3 or 4 nonhematologic toxicities were nausea, vomiting, and diarrhea, each of which complicated 7% of all cycles. Twenty-one patients were evaluable for response to induction CIP. Five patients had a partial response (response rate of 24%, 95% confidence interval [CI]: 8–47%), and the remaining 16 patients had stable disease (stable disease rate of 76%, 95% CI: 53–92%). Of note, no patients experienced disease progression during the first two cycles. The median prechemotherapy GTV was 98 mL (range, 6–305 mL), and the median postchemotherapy GTV was 64 mL (range, 6–215 mL). This represents a reduction in the median GTV of 35%.

Concurrent Chemoradiation Toxicity

Twenty-one patients initiated the concurrent chemoradiation, and 20 patients completed therapy. One patient developed a pulmonary embolism and became supratherapeutic on anticoagulation and developed a hemorrhagic pericardial effusion and did not complete the concurrent chemoradiotherapy to 74 Gy. The primary toxicities were grade 3 esophagitis (19.5%), and cardiac arrhythmia due to atrial fibrillation (9.5%) (Table 3). Twelve patients initiated the maintenance gefitinib before the amendment, and patients received a median of 2 months of maintenance gefitinib (range, 1–4 months). Three patients developed late complications, defined as developing or persisting >60 days after completion of radiation therapy (grade 3 esophageal [$n = 2$]; grade 3 anterior spinal cord syndrome due to probable spinal cord infarct [$n = 1$]) within the radiation field. The patient presented with anterior spinal cord syndrome 8 months after completion 3-dimensional TCRT and 2 weeks after discontinuing gefitinib. She presented with symptoms of lower extremities weakness and tingling for 1 to 2 months and new onset urinary retention. The patient received radiation therapy dose at the maximum point of 4708 cGy from the APPA fields, and the total delivered including the scatter dose from the oblique fields was 4957 cGy. The patient was evaluated with magnetic resonance imaging of the spine, which was negative for cord compression, a lumbar puncture, which was negative for malignant cells, B12 and folate were within normal limits, and rapid plasma regain and hypercoaguable work-up was negative.

TABLE 2. Toxicity of Induction Chemotherapy[a] (43 Cycles)

	Toxicity Grade	
	3	4
Hematologic		
Neutropenia	2	0
Thrombocytopenia	2	0
Hemoglobin	0	0
Febrile neutropenia	0	0
Nonhematologic		
Nausea	7	0
Vomiting	7	0
Diarrhea	7	0
Hypomagnesemia	2	0
Hypersensitivity reactions	0	2

[a] Numbers represent percentage of cycles in which the toxicity occurred.

TABLE 3. Acute Toxicity During Concurrent Chemotherapy

	Toxicity Grade	
	3	4
Hematologic		
Neutropenia	19	0
Thrombocytopenia	9.5	4.8
Hemoglobin	9.5	0
Febrile neutropenia	0	0
Nonhematologic		
Esophagitis	9.5	0
Arrhythmia[a]	9.5	0
Pneumonitis[b]	4.8	0
Infection[c]	4.8	0
Diarrhea	4.8	0
Fatigue	4.8	0
Syncope	4.8	0
Pericardial effusion[d]	4.8	0
Elevated prothrombin time[d]	4.8	0
Embolism[d]	0	4.8
Hematemesis	4.8	0

All values reported are in percentages.
[a] Atrial fibrillation in both cases.
[b] Determined to be radiation induced pneumonitis.
[c] Infection without neutropenia (herpes simplex virus meningoencephalitis).
[d] All these events occurred in a single patient.

Progression-Free and Overall Survival

Of a total of 23 patients who had been followed for survival information, 19 have died and 4 were still alive at the time of analysis (Figure 1). Three survivors were alive more than 30 months out from the date of the start of treatment. The median follow-up time for survivors was 30 months. Of the 19 patients who have died, 15 have been documented to have progressed earlier, and 4 have died without evidence of progression. A total of 20 have either progressed or died

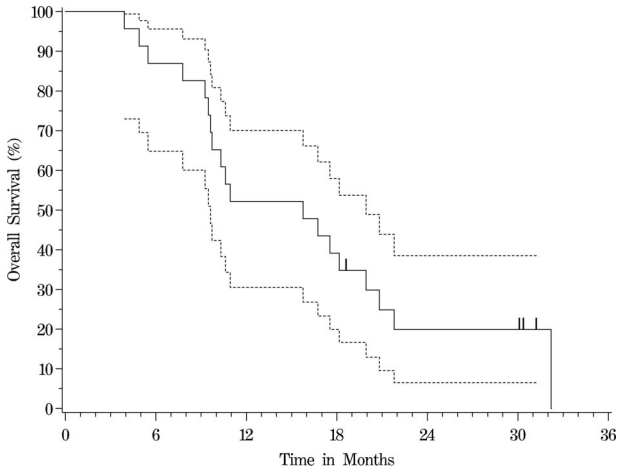

FIGURE 1. Overall survival with 95% confidence intervals.

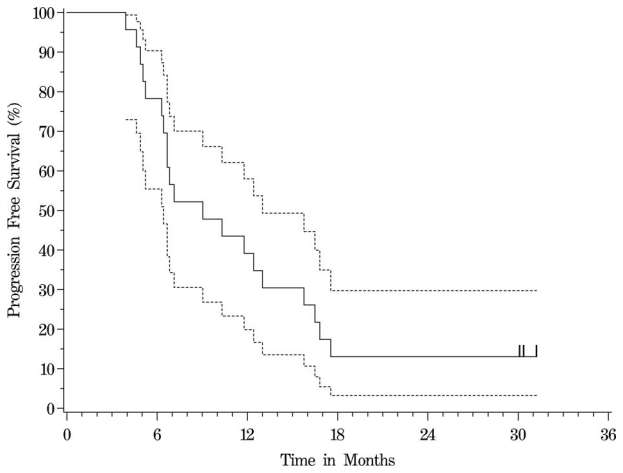

FIGURE 2. Progression-free survival with 95% confidence intervals.

(Figure 2). Median progression-free survival time was 9 months (95% CI: 7–13 months), and median overall survival time was 16 months (95% CI: 10–20 months). Three patients experienced local progression, one patient experienced local and distant progression, and 11 patients experienced distant progression.

DISCUSSION

This trial did meet the primary end-point of demonstrating that gefitinib can safely be integrated into combined modality therapy without excessive toxicity or a significant number of patients failing to complete the prescribed treatment. However, the median survival time was disappointing in comparison to our previous trial and the recent trials that have used a similar treatment paradigm (Table 4).[5,22–25] A recent retrospective analysis of patients ($n = 112$) treated on 4 of our phase I/II or II combined revealed a median survival of 24 months (95% CI: 18–31 months) and 5-year survival rate of 24% (95% CI: 16–33%).[26] The increased use of PET scans (91% of patients) alone on this trial should have in improved survival due to superior staging techniques in comparison to our previous trials. The eligibility criteria are similar to our previous trials, which should have reduced the chance of any significant differences in the patient population on this trial from our previous trials. However, other unrecognized prognostic factors or changes in physician patient selection may have influenced enrollment and contributed the lower than expected survival, especially given the relatively small size of the trial. Of note, 4 of the 23 enrolled on this trial had ≥5% weight loss, which has been identified as a poor prognostic factor in combined modality trials.[24] Importantly, this trial differs from standard therapy is several aspects: the use of a more aggressive three drug induction therapy, the use of pegfilgastrim supportive therapy, increased dose of TCRT (74 Gy while the standard dose was 60 Gy), and the use of gefitinib concurrent with TCRT. It is difficult to determine whether one or a combination of these factors may have adversely impacted the survival.

One concern is that the treatment with gefitinib adversely impacted the survival of patients on this trial. At the same time, this trial was being performed SWOG, Cancer and Leukemia Group B (CALGB), and Australian centers were performing trials with gefitinib in combination combined modality therapy (Table 5).[27–29] Patients on the SWOG trial

TABLE 4. Recent Trials of Induction Chemotherapy Followed by Concurrent Chemoradiotherapy

Trial	*N*	Induction Chemotherapy	Concurrent Chemotherapy	TRT Dose (Gy)	Median Survival (mo)
LCCC 9603[5]	62	Carboplatin/paclitaxel	Carboplatin/paclitaxel weekly	60–74	24
LCCC 2001[8]	29	Carboplatin/paclitaxel + irinotecan	Carboplatin/paclitaxel weekly	78–90	24
CALGB 39801[24]	366	Arm A – none	Carboplatin/paclitaxel weekly	66	12
		Arm B – carboplatin/paclitaxel	Carboplatin/paclitaxel weekly		14
CALGB 30105[37]	69[a]	Arm A – carboplatin/paclitaxel	Carboplatin/paclitaxel weekly	74	24
		Arm B – carboplatin/gemcitabine	Gemcitabine twice/wk		14
BCTG[25]	276	Carboplatin/paclitaxel	RT alone	60	14.1
			Paclitaxel weekly		18.7
RTOG 98-01[23]	243	Carboplatin/paclitaxel	Carboplatin/paclitaxel weekly	69.6[b]	17.5

[a] Forty-three patients on Arm A, 26 patients on Arm B. Arm B closed early due to excessive toxicity.
[b] TRT = 69.6 Gy at 1.2 Gy BID.
CALGB, Cancer and Leukemia Group B; LCCC, Lineberger Comprehensive Cancer Center; BCTG, Bronchial Carcinoma Therapy Group; RTOG, Radiation Therapy Oncology Group; TRT, Thoracic Radiation Therapy.

TABLE 5. Combined Modality Trials with Gefitinib

Trial	*N*	Chemotherapy or Induction Therapy	TRT Dose	Concurrent or Maintenance Therapy	Median Survival
SWOG 0023[28]	571	Cisplatin/etoposide with concurrent TRT followed by docetaxel for 3 cycles	61	Maintenance	
				Gefitinib (n = 118)	23 mo[a]
				Placebo (n = 125)	35 mo
				Concurrent therapy	
CALGB[27]	59[b]	Carboplatin/paclitaxel gefitinib	66	Stratum 1 gefitinib	19 mo
				Stratum 2 gefitinib daily, weekly carboplatin/paclitaxel	12 mo
Australian[29]	28	None	60	Concurrent therapy	NR[d]
				Gefitinib daily, weekly carboplatin/paclitaxel[c]	

[a] Median Survival time from randomization to gefitinib placebo (ie, after completion of concurrent chemoradiotherapy and 3 cycles of consolidation docetaxel).
[b] Stratum 1 (n = 20), stratum 2 (n = 39). Stratum 1 defined as PS 0–1 with > 5% weight loss or PS = 2; stratum 2 PS 0–1 with <5% weight loss.
[c] Chemotherapy dose escalation trials with all cohorts receiving gefitinib 250 mg daily; cohort 1 carboplatin (AUC = 2) weekly alone, cohorts 2, 3, and 4 carboplatin (AUC = 2) weekly and paclitaxel 25, 35, 45 mg/m^2 weekly, respectively. Cohort 4 expanded to 16 patients.
[d] Median survival has not been reached, survival at 24 mo follow-up was 60% (95% confidence intervals: 39–82%).
SWOG, Southwest Oncology Group; CALGB, Cancer and Leukemia Group B; TRT, Thoracic Radiation Therapy; NR, not reached.

were treated with concurrent chemoradiotherapy and consolidation docetaxel, and were then randomized to maintenance gefitinib (n = 118) or placebo (n = 125). With a median follow-up of 27 months patients randomized to the gefitinib arm had a worse overall survival than the placebo arm: overall survival from time of randomization 23 versus 35 months, respectively (p = 0.01). The primary cause of the poor survival on the gefitinib arm was an excessive number of deaths due to progressive disease. There did not appear to be any difference in the baseline characteristics between the two treatment arms at time of randomization. On our trial, only 12 patients of the 23 patients received maintenance gefitinib for a median of 2 months (range, 1–4 months); thus, it is difficult to determine whether maintenance gefitinib contributed to the disappointing survival on our trial.

The CALGB trial was a phase II trial with two cohorts, and patients were stratified based on clinical characteristics (stratum 1 and 2).[27] This trial was closed after the interim results of SWOG 0023 were announced. The patients on stratum 2 (n = 39) were a similar patient population and received a similar treatment to the patients on our trial; the median progression-free survival was 9.2 months, 1-year survival rate was 47%, and median overall survival was 12 months. An Australian multicenter phase I trial investigated the combination of thoracic radiation therapy (60 Gy) and gefitinib 250 mg daily with carboplatin (AUC = 2) weekly in the first cohort, and gefitinib 250 mg daily, carboplatin (AUC = 2) weekly and escalating doses of paclitaxel (25, 25, 45 mg/m^2) weekly on cohorts 2, 3, and 4, respectively.[29] All patients were required to have stage III disease, good functional status, and weight loss <10%. No dose-limiting toxicities were observed, and all patients received 60 Gy. A total of 28 patients were enrolled, and the fourth cohort (gefitinib 250 mg daily, carboplatin (AUC = 2) weekly, and paclitaxel 45 mg/m^2 weekly) was expanded (n = 16). The median survival for all patients on the trial has not been reached, and the 2-year survival rate is 60% (95% CI: 39–82%).

The increased number of cancer deaths seen on the SWOG trial and the relatively low median survival times on our and the CALGB trials is concerning. The combination of treatment with radiation therapy and concurrent gefitinib or subsequent gefitinib may fundamentally alter the biology of the NSCLC. Several groups have demonstrated the development of "acquired resistance" due to the development of a secondary mutation resulting in threonine to methionine at 790 (T790M) of EGFR.[30–32] This mutation has been reported to be present at the time of diagnosis in some patients as well.[33] Preclinical and anecdotal clinical evidence indicates that tumors with this mutation may have a more aggressive behavior.[34,35] Focal amplification of the MET proto-oncogene has also been detected in lung cancer specimens from patients who were initially demonstrated a partial response to gefitinib or erlotinib and subsequently developed resistance.[36] The amplification the MET gene caused activation of the HER3-dependent intracellular pathways leading to the resistance. These changes and potentially other molecular changes related to the treatment may have altered the clinical course or the effectiveness of subsequent therapies of NSCLC in patients on this trial.

Preclinical models have investigated EGFR-TKI and the anti-EGRR monoclonal antibody C225 therapy in combination with radiation.[37,38] Treatment with the C225 alone and in combination with radiation therapy resulted in a significant prolongation of tumor growth delay and local control in comparison to control tumors. Treatment with EGFR-TKI resulted in reduction of tumor volume, but did not improve local control in comparison to control tumors. This preclinical data suggests that anti-EGFR antibody direct therapy may be more effective in combination with radiation therapy than EGFR-TKI therapy in combination with radiation therapy. The Radiation Therapy Oncology Group recently performed a phase II trial of cetuximab (C225) in combination with weekly carboplatin (AUC = 2) and paclitaxel (45 mg/m^2), followed by two cycles of carboplatin (AUC = 6) and paclitaxel (200 mg/m^2) every 3 weeks.[39] Ninety-three patients have been enrolled and 87 are evaluable, and median follow-up of 17.6 months. The 18-month overall survival is 54.7%, and the primary toxicities were grade 4 hematologic toxicities and grade 3 esophagitis. Further follow-up and additional trials will be required to deter-

mine the toxicity and efficacy of EGFR directed antibodies in stage III disease.

Our current trial did use the treatment paradigm of induction chemotherapy, and the recent CALGB trial 39801 revealed a similar survival between concurrent chemoradiotherapy and induction chemotherapy followed by concurrent chemoradiotherapy (Table 4).[24] The survival on both treatment arms was lower than the survival seen on the previous CALGB trial and other trials that employed induction chemotherapy. It is possible that as concurrent chemoradiotherapy within the United States has been become more widely accepted the patient population enrolled on stage III clinical trials has expanded to include patients who physicians previously would not have considered for this treatment paradigm, and this contributed to the lower survival than previous trials. The inclusion of patients with significant weight loss may have adversely impacted the overall survival results of this trial; 17% of patients enrolled on this trial had 5 to 10% weight loss, and 9% had >10% weight loss. Patients who had weight loss >5% and who were otherwise eligible ($n = 87$) on the concurrent chemoradiotherapy and induction chemotherapy and concurrent chemoradiotherapy arms had a median survival of 8 and 10 months, respectively, and 3-year survival rate of 10% and 23%, respectively. The prevalence of patients with significant weight loss may significantly influence the outcome of small phase II trials of combined modality therapy.

Recent meta-analyses in the advanced NSCLC revealed that cisplastin-based treatments have a superior overall survival, but a higher rate of toxicity when compared to carboplatin-based treatments.[40,41] In stage III disease, the use of cisplatin-based therapy may provide more effective treatment for occult micrometastatic disease. The Hoosier Oncology Group recently performed a phase III trial in which patients received cisplatin and etoposide and thoracic radiation therapy to 59.4 Gy, followed by randomization to consolidation docetaxel versus observation.[42] The median survival for all patients was 21 months, and there was no significant difference in the median survival between the observation and consolidation chemotherapy arm (24.2 versus 21.6 months, respectively; $p = 0.94$). The numerically longer survival on the Hoosier Oncology Group than on CALGB 39801, the potential advantages of concurrent systemic therapy with thoracic radiation, and the data from meta-analyses from advanced stage disease raises the possibility that cisplatin-based treatment paradigms may be superior in stage III disease. A phase III trial specifically designed to compare cisplatin-based and carboplatin-based therapy would be required to definitively investigate this clinical question.

CONCLUSION

Induction chemotherapy with carboplatin, irinotecan, and paclitaxel followed by concurrent carboplatin, paclitaxel, and gefitinib and 3-dimensional TCRT to 74 Gy is feasible with an acceptable toxicity profile. However, the survival on this trial was disappointing in comparison to the survival seen on our previous trials.

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
2. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. *Chest* 2005;128:452–462.
3. Bulzebruck H, Bopp R, Drings P, et al. New aspects in the staging of lung cancer. Prospective validation of the International Union Against Cancer TNM classification. *Cancer* 1992;70:1102–1110.
4. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology Treatment of Unresectable Non-Small Cell Lung Cancer Guideline: Update 2003. *J Clin Oncol* 2004;22:330–353.
5. Socinski M, Rosenman J, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B non-small cell lung carcinoma: a modified phase I/II trial. *Cancer* 2001;92:1213–1223.
6. Socinski M, Halle JS, Morris DE, et al. Long-term results of aggressive combined modality therapy employing induction and concurrent carboplatin/paclitaxel with dose-escalated thoracic conformal radiation therapy. *Lung Cancer* 2003;41:S239.
7. Stinchcombe TE, Morris DE, Moore DT, et al. Post-chemotherapy gross tumor volume is predictive of survival in patients with stage III non-small cell lung cancer treated with combined modality therapy. *Lung Cancer* 2006;52:67–74.
8. Socinski M, Morris, David E, et al. Induction and concurrent chemotherapy with high-dose conformal radiation therapy in unresectable stage IIIA/B non-small cell lung cancer: a dose escalation phase I trial. *J Clin Oncol* 2004;22:4341–4350.
9. Socinski M, Sandler A, Israel V, et al. Phase II trial of irinotecan, paclitaxel, and carboplatin in patients with previously untreated stage IIIB/IV non-small cell lung cancer. *Cancer* 2002;95:1520–1527.
10. Socinski M, Sandler A, Miller L, et al. Phase I trial of the combination of irinotecan (CPT-11), paclitaxel, and carboplatin in patietns with advanced non-small cell lung cancer. *J Clin Oncol* 2001;19:1078–1087.
11. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003;21:2237–2246.
12. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003;290:2149–2158.
13. Solomon B, Hagekyriakou J, Trivett MK, et al. EGFR blockade with ZD1839 ("Iressa") potentiates the antitumor effects of single and multiple fractions of ionizing radiation in human A431 squamous cell carcinoma. Epidermal growth factor receptor. *Int J Radiat Oncol Biol Phys* 2003;55:713–723.
14. Bianco C, Tortora G, Bianco R, et al. Enhancement of antitumor activity of ionizing radiation by combined treatment with the selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa). *Clin Cancer Res* 2002;8:3250–3258.
15. Ochs JS. Rationale and clinical basis for combining gefitinib (IRESSA, *ZD1839*) with radiation therapy for solid tumors. *Int J Radiat Oncol Biol Phys* 2004;58:941–949.
16. Kim DW, Choy H. Potential role for epidermal growth factor receptor inhibitors in combined-modality therapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59:11–20.
17. Calvert A, Newell D, Gumbrell L, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;7:1748–1756.
18. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 2. *J Clin Oncol* 2004;22:785–794.
19. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 1. *J Clin Oncol* 2004;22:777–784.

20. Kelly K, Gaspar L, Chansky K, et al. Low incidence of pneumonitis on SWOG 0023: preliminary analysis of an ongoing phase III trial of concurrent chemoradiotherapy followed by consolidation docetaxel and Iressa/Placebo maintenance in patients with inoperable stage III non-small cell lung cancer. *J Clin Oncol* 2005;23: Abstract 7058.
21. World Health Organization. WHO Handbook for Reporting Results of Cancer treatment. WHO Offset Publication No. 48. Geneva, Switzerland: World Health Organization, 1979.
22. Blackstock AW, Socinski MA, Bogart J, et al. Induction (Ind) plus concurrent (Con) chemotherapy with high-dose (74 Gy) 3-dimensional (3-D) thoracic radiotherapy (TRT) in stage III non-small cell lung cancer (NSCLC): Preliminary report of Cancer and Leukemia Group B (CALGB) 30105. *ASCO Meeting Abstr* 2006;24:abstract7042.
23. Movsas B, Scott C, Langer C, et al. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98–01. *J Clin Oncol* 2005;23:2145–2154.
24. Vokes EE, Herndon JE II, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol* 2007;25:1698–1704.
25. Huber RM, Flentje M, Schmidt M, et al. Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. *J Clin Oncol* 2006;24:4397–4404.
26. Lee CB, Socinski MA, Lin L, et al. High-dose 3D chemoradiotherapy trials in stage III non-small cell lung cancer (NSCLC) at the University of North Carolina: Long-term follow up and late complications. *ASCO Meeting Abstr* 2006;24:abstract7145.
27. Ready N, Janne P, Herndon J, et al. Chemoradiotherapy (CRT) and gefitinib (G) in stage III non-small cell lung cancer (NSCLC): A CALGB stratified phase II trial. *ASCO Meeting Abstr* 2006;24: abstract7046.
28. Kelly K, Chansky K, Gaspar LE, et al. Updated analysis of SWOG 0023: A randomized phase III trial of gefitinib versus placebo maintenance after definitive chemoradiation followed by docetaxel in patients with locally advanced stage III non-small cell lung cancer. *ASCO Meeting Abstr* 2007;25:abstract7513.
29. Ball D, Burmeister B, Mitchell P, et al. Phase I trial of gefitinib in combination with concurrent carboplatin, paclitaxel and radiation therapy in patients with stage III non small cell lung cancer ("CRITICAL"): P2-162. *J Thoracic Oncol* 2007;2:S633–S634.
30. Kosaka T, Yatabe Y, Endoh H, et al. Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. *Clin Cancer Res* 2006;12:5764–5769.
31. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005;2:e73.
32. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2005;352:786–792.
33. Shih JY, Gow CH, Yang PC. EGFR mutation conferring primary resistance to gefitinib in non-small-cell lung cancer. *N Engl J Med* 2005;353:207–208.
34. Toyooka S, Kiura K, Mitsudomi T. EGFR mutation and response of lung cancer to gefitinib. *N Engl J Med* 2005;352:2136 (author reply).
35. Vikis H, Sato M, James M, et al. EGFR-T790M is a rare lung cancer susceptibility allele with enhanced kinase activity. *Cancer Res* 2007;67: 4665–4670.
36. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;316:1039–1043.
37. Krause M, Schutze C, Petersen C, et al. Different classes of EGFR inhibitors may have different potential to improve local tumour control after fractionated irradiation: a study on C225 in FaDu hSCC. *Radiother Oncol* 2005;74:109–115.
38. Krause M, Prager J, Zhou X, et al. EGFR-TK inhibition before radiotherapy reduces tumour volume but does not improve local control: differential response of cancer stem cells and nontumourigenic cells? *Radiother Oncol* 2007;83:316–325.
39. Blumenschein GR, Moughan J, Curran W, et al. A phase II study of cetuximab (C225) in combination with chemoradiation: B3-07. *J Thorac Oncol* 2007;2(Suppl 4):S342–S343.
40. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst* 2007;99:847–857.
41. Hotta K, Matsuo K, Ueoka H, et al. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22:3852–3859.
42. Hanna NH, Neubauer M, Ansari R, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01–24/ USO-023. *J Clin Oncol*. 2007 *ASCO Annual Meeting Proc Part I* 2007;25: abstract 7512.

