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ORIGINAL REPORT

Combined Chemoradiotherapy Regimens of Paclitaxel and Carboplatin for Locally Advanced Non–Small-Cell Lung Cancer: A Randomized Phase II Locally Advanced Multi-Modality Protocol

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose

This phase II noncomparative randomized trial was conducted to determine the optimal sequencing and integration of paclitaxel/carboplatin with standard daily thoracic radiation therapy (TRT), in patients with locally advanced unresected stage III non–small-cell lung cancer (NSCLC). Survival data were compared with historical standard sequential chemoradiotherapy data from the Radiation Therapy Oncology Group.

Patients and Methods

Patients with unresected stages IIIA and IIIB NSCLC, with Karnofsky performance status ≥ 70% and weight loss ≤ 10%, received two cycles of induction paclitaxel (200 mg/m^2)/carboplatin (area under the plasma concentration time curve [AUC] = 6) followed by TRT 63.0 Gy (arm 1, sequential) or two cycles of induction paclitaxel (200 mg/m^2)/carboplatin (AUC = 6) followed by weekly paclitaxel (45 mg/m^2)/carboplatin (AUC = 2) with concurrent TRT 63.0 Gy (arm 2, induction/concurrent), or weekly paclitaxel (45 mg/m^2)/carboplatin (AUC = 2)/TRT (63.0 Gy) followed by two cycles of paclitaxel (200 mg/m^2)/carboplatin (AUC = 6; arm 3, concurrent/consolidation).

Results

With a median follow-up time of 39.6 months, median overall survival was 13.0, 12.7, and 16.3 months for arms 1, 2, and 3, respectively. During induction chemotherapy, grade 3/4 granulocytopenia occurred in 32% and 38% of patients on study arms 1 and 2, respectively. The most common locoregional grade 3/4 toxicity during and after TRT was esophagitis, which was more pronounced with the administration of concurrent chemoradiotherapy on study arms 2 and 3 (19% and 28%, respectively).

Conclusion

Concurrent weekly paclitaxel, carboplatin, and TRT followed by consolidation seems to be associated with the best outcome, although this schedule was associated with greater toxicity.

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INTRODUCTION

In the United States, lung cancer continues to be the leading cause of cancer-related deaths for both men and women.[1] Non–small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases.[2] Approximately 40% of NSCLC patients present with stages IIIA and IIIB disease.[3]

Thoracic radiation therapy (TRT) has been the traditional treatment approach for patients with unresected stages IIIA and IIIB NSCLC. Although TRT provides effective symptom relief and contributes to locoregional tumor control, 5-year survival rates with TRT alone are disappointing.[4-6] The combination of TRT with chemotherapy has demonstrated superiority over TRT alone.[7-14]

Radiation Therapy Oncology Group (RTOG) 88-08 compared three regimens of TRT as follows: (1) standard TRT; or (2) sequential chemotherapy and TRT; or (3) sequential chemotherapy and hyperfractionated TRT in a phase III trial. The second schedule (sequential chemotherapy and TRT) produced the best median survival of 13.2 months.[9]

Recently, two randomized studies that compared concurrent versus sequential chemoradiotherapy found that the concurrent approach provides superior outcome.[15,16] Both randomized trials evaluated second-generation cisplatin combinations with TRT.[7-16] Subsequently, newer chemotherapeutic agents, such as paclitaxel,[17] have been successfully integrated with TRT in combined modality programs.[3,18-19] Pilot studies that evaluated weekly regimens of paclitaxel and carboplatin with TRT for patients with locally advanced NSCLC provided encouraging safety, efficacy, and tolerability results. However, the therapeutic benefit of either induction or consolidation full-dose chemotherapy in conjunction with concurrent chemoradiotherapy is not well defined. The pattern of failure with these approaches has also not been well established from these small phase II trials.[18,19] This phase II randomized three-arm study was conducted for patients with locally advanced unresected stage III NSCLC to determine the optimal schedule sequence of paclitaxel and carboplatin when administered in combination with TRT.

PATIENTS AND METHODS

Patient Eligibility

Histologic or cytologic determination of stage IIIA or IIIB NSCLC (including squamous cell carcinoma, adenocarcinoma, large cell anaplastic carcinoma, and poorly differentiated NSCLC) was required. Patients with T1-T3 with N2 disease if medically inoperable, T4 with any node size and extent, and those with N3 disease with any tumor involvement were eligible. Patients were required to have measurable disease; those with significant pleural effusions seen on chest x-ray were not eligible.

Additional eligibility criteria included patient age $\geq$ 18 years, Karnofsky performance status (KPS) $\geq$ 70%, weight loss $\leq$ 10% in the 3 months before diagnosis, no prior systemic chemotherapy, no prior radiation therapy to the thorax or total surgical resection, granulocyte count $\geq$ 2,000/mL, platelet count $\geq$ 100,000/mL, hemoglobin more than 8 mg/dL, bilirubin less than 1.5$\times$ normal, creatinine clearance more than 50 mL/min, and forced expiratory volume in 1 second (FEV_1) more than 800 mL. Patients were also required to have a magnetic resonance imaging (MRI) or computed tomography (CT) brain scan within the 4 weeks before study entry to rule out asymptomatic brain metastases. Patients with active concurrent malignancy, serious medical or psychiatric illness, or history of serious cardiac disease were excluded.

The protocol was approved by the institutional review boards with jurisdiction over each site at which patients were registered, and all patients gave written informed consent before enrollment.

Two weeks before study entry, complete documentation of medical history and a physical exam of all patients was taken, which included: weight, performance status, WBCs/granulocytes, hemoglobin, platelet count, AST, ALT, alkaline phosphatase, total bilirubin, albumin, glucose, and creatinine (24 hour or calculated clearance). Pulmonary function tests and an ECG were performed on patients before study entry. Within 4 weeks of study entry, prestudy radiographic assessments, such as CT scans and bone scans, were obtained to document tumor staging for eligibility. CT scans were used consistently for all evaluations and tumor measurements during the entire study period. Women of childbearing potential had to have a negative urine or serum pregnancy test within the 7 days before study entry.

Treatment Schedules

Patients were randomly assigned to one of three treatment arms: arm 1 (sequential), sequential chemotherapy followed by thoracic radiation therapy; arm 2 (induction/concurrent), induction chemotherapy followed by concurrent chemoradiotherapy; arm 3 (oncurrent/consolidation), concurrent chemoradiotherapy followed by consolidation chemotherapy (Fig 1).

Arm 1. Sequential chemotherapy consisted of two 3-week cycles of paclitaxel 200 mg/m^2 administered over 3 hours, immediately followed by carboplatin at an area under the plasma concentration time curve (AUC) = 6 mg/mL $\cdot$ min as an intravenous infusion over 30 minutes. The dose of carboplatin was calculated using the Calvert formula with the creatinine clearance estimated using the Cockroft-Gault equation.[20] TRT was initiated on day 42 and consisted of 1.8 Gy daily, five times per week (45.0 Gy target dose in 5 weeks to the initial field), followed by a total of 18.0 Gy fractions delivered at 2.0 Gy fractions daily to the initial tumor volume with reduced fields (total dose, 63.0 Gy in 34 fractions over 7 weeks), but including enlarged lymph nodes $\geq$ 2.0 cm.

Arm 2. Patients on the induction/concurrent arm received the same chemotherapy as patients on arm 1. After completing two cycles of chemotherapy they were begun on TRT administered concurrently with weekly paclitaxel 45 mg/m^2 via intravenous infusion over 1 hour, followed by carboplatin dose targeted to

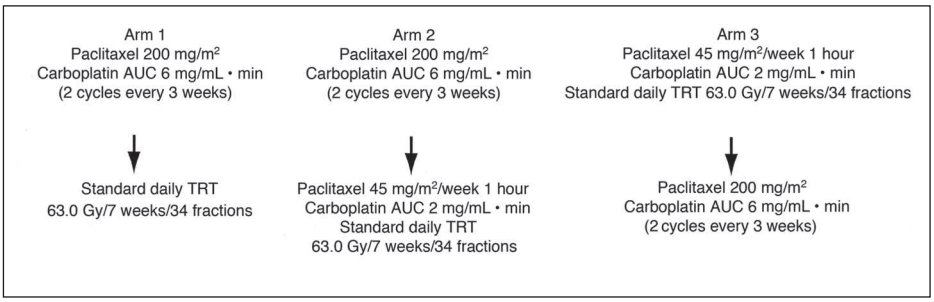

Fig 1. Treatment scheme for the three study arms in locally advanced multimodality protocol. AUC, area under the plasma concentration time curve; TRT, thoracic radiation therapy.

achieve an AUC = 2 mg/mL · min over 30 minutes, and TRT as the patients in arm 1.

Arm 3. On the concurrent/consolidation arm, concurrent chemoradiotherapy as administered to patients in arm 2 was administered first, followed by consolidation chemotherapy. The consolidation consisted of two cycles initiated 3 to 4 weeks after completion of concurrent therapy, and the doses were the same as the induction regimens in arms 1 and 2.

Treatment Modifications

On arm 1, therapy was delayed for 1 week if the granulocyte count was less than 1.5 × 103/mL and/or the platelet count was less than 50 × 103/mL on the day of treatment. Thereafter, patients received chemotherapy at a 25% dose reduction. If granulocyte counts remained less than 1.5 × 103/mL or platelet counts less than 50 × 103/mL for more than 1 week, chemotherapy treatment was permanently discontinued. Patients underwent imaging studies for disease evaluation and TRT was administered when the patient's bone marrow had recovered.

During chemoradiotherapy on arms 2 and 3, the chemotherapy dose was reduced by 50% if the granulocyte count dropped from 1.0 to 1.49 × 10^3 granulocytes/mL and/or the platelet count dropped to 50 to 74.9 × 10^3 platelets/mL. If the granulocyte count fell below 1.0 × 10^3/mL and platelet count to less than 50 × 10^3/mL, the chemotherapy dose was omitted. Dose reductions for chemotherapy (induction or consolidation) were made as described for arm 1.

In any of the assigned treatment arms, when a chemotherapy dose reduction was required, re-escalation of the chemotherapy dose was performed for subsequent doses during that specific course. In addition, on study arms 2 or 3, any dose reduction was not carried over to the next scheduled course unless deemed necessary by the investigator. Any patient unable to tolerate the 50% dose reduction of chemotherapy was taken off the study.

Radiotherapy

The TRT target volume for arms 1 and 2 was the postchemotherapy tumor volume, and for arm 3 it was based on the original tumor volume. Deviations from the daily TRT dose of up to 5% were allowed. Radiation therapy interruptions or delays were permitted only for febrile neutropenia or grade 4 esophagitis/mucositis. If radiation therapy interruptions of 1 week (5 consecutive days) occurred, TRT was to be completed to the prescribed dose. Radiation therapy planning and compliance per protocol specifications were centrally reviewed for all patients.

Assessment of Efficacy and Safety

The primary objective of this study was to compare the median survival time associated with each dose schedule with a median survival time of 13.7 months. Because of protocol similarities, the median survival from the RTOG 88-08 study, 13.7 months, was deemed an appropriate benchmark for our study. RTOG 88-08 used a chemoradiotherapy regimen of cisplatin 100 mg/m^2 on days 1 and 29 and vinblastine 5 mg/m^2 once per week for 5 consecutive weeks beginning on day 1, followed by TRT to a total dose of 60 Gy in 30 fractions over 6 weeks starting on day 60.[9]

Progression-free survival (defined as the time from start of treatment to death or progression) was a secondary study end point. Safety of the three regimens was evaluated by determining the frequency of severe (≥ grade 3) toxicities based on the National Cancer Institute Common Toxicity Criteria and RTOG Acute Morbidity Criteria.

Statistical Analysis

The primary objective of this phase II randomized study was survival. For analyses, each arm was compared with a historical control using the sequential chemoradiotherapy arm (arm 2) of the RTOG 88-08 trial, for which the available reported median survival time was 13.7 months. Using a one-sided significance level of .05 and statistical power of 80%, 84 assessable patients were required to be randomly assigned to each arm in order to detect at least a 45% improvement (20.0 months *v* 13.7 months) in median survival over historical control. Each treatment arm was compared with historical control with at least 80% statistical power to detect an estimated median survival time of 20.0 months or longer. In order to maintain the statistical integrity of the study, a provision of four additional patients per arm was allowed in case of ineligibility.

Statistical analysis of overall survival compared with historical control was performed using a one-sided log-rank of Kaplan-Meier survival estimates. The duration of survival was calculated from the date of randomization until death or last known follow-up. Results were considered significant at the 5% level ($P < .05$).

A Triangle Test was used to determine which, if any, arm(s) should be discontinued due to a low likelihood of benefit compared to a historical control.

RESULTS

Patient Characteristics

Between February 1998 and June 2001, 276 patients were enrolled onto the study from 49 academic centers and community hospitals in the United States. As accrual to this phase II study reached the projected number of patients, an interim statistical analysis using the triangle test was applied to all three arms. Arm 2 was closed to accrual due to the low likelihood of benefit compared with historical control. Sample sizes in arms 1 and 3 were expanded to accommodate a phase III design. Subsequently, when data from the RTOG 9410 study became available and confirmed the benefit of concurrent therapy, accrual to the present study decreased and the study was permanently closed to accrual. The date of final analysis was May 25, 2004.

Of the 276 patients enrolled, 19 patients were excluded from the final analysis; 18 due to ineligibility, and one patient due to not receiving study therapy. Reasons for ineligibility included stage IV disease (n = 3), M1 disease (n = 2), bone metastases (n = 2), cervical node metastases (n = 1), stage I disease (n = 1), prior chemotherapy (n = 1), no prestudy brain CT/MRI (n = 1), more than 10% weight loss (n = 1), no prestudy bilirubin (n = 1), pleural and pericardial effusion that was malignant (n = 1), prestudy creatinine clearance of 38 mL/min (n = 1), no prestudy absolute neutrophil count (n = 1), FEV_1 less than 800 mL (n = 1), and no N2 status documentation (n = 1). A total of 257 eligible patients (arm 1, n = 91; arm 2, n = 74; arm 3, n = 92) were, therefore, evaluated for efficacy as measured by overall survival and safety.

Patient baseline characteristics were comparable across all three treatment arms (Table 1). There was a higher

Table 1. Patient Characteristics

Characteristic	Arm 1 (n = 91) (CT → RT)		Arm 2 (n = 74) (CT → CT + RT)		Arm 3 (n = 92) (RT + CT → CT)		P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
No. of patients ineligible	6		6		7		
Age, years							.43
< 70	73	80	53	72	69	75	
70+	18	20	21	28	23	25	
Sex							
Male	63	69	54	73	62	67	
Female	28	31	20	27	30	33	
KPS							.59
70	7	8	5	7	2	2	
80-100	84	92	69	93	90	98	
Weight loss, %							.40
< 5%	66	73	47	64	66	72	
5-10%	25	27	27	36	26	28	
Histology							
Squamous	38	42	24	32	37	40	
Adenocarcinoma	32	35	25	34	32	35	
Large cell	9	10	11	15	9	10	
Combined squamous and adenocarcinoma	1	1	3	4	2	2	
Carcinoma NOS	9	10	11	15	11	12	
Other/unknown	2	2	0	0	1	1	
AJCC stage							
IIIA	33	36	27	36	35	38	
IIIB	58	64	47	64	57	62	

Abbreviations: CT, chemotherapy; RT, radiotherapy; KPS, Karnofsky performance status; NOS, not otherwise specified; AJCC, American Joint Committee on Cancer.
*Kruskal-Wallis test.

percentage of men than women in each treatment arm and the majority of patients was younger than 70 years old. Approximately one third of patients in each arm had a 5% to 10% weight loss within the 3 months before diagnosis and two thirds of patients entered the study with stage IIIB disease. Mean hemoglobin levels at baseline were 13.15, 13.38, and 13.66 for arms 1, 2, and 3, respectively. Although there were no statistical differences, there were some minor imbalances between arms. The majority of patients in each arm had a baseline performance status of 80 to 100, with only 8% (arm 1), 7% (arm 2), and 2% (arm 3) of patients with a performance status of 70. When evaluated based on KPS 70 to 80 and 90 to 100, there were more patients in arm 2 with KPS 70 to 80 (31%) compared with the other arms (arm 1, 27%; arm 3, 24%). Similarly, 73% of patients enrolled onto arm 2 were men, compared with 69% of the patients on arm 1% and 67% on arm 3. Percentage of weight loss also differed between arms with a higher incidence of 5% to 10% weight loss in arm 2 (36%) compared with arm 1 (27%) and arm 3 (28%).

Treatment Administration

Overall, in treatment arms 1, 2, and 3, 70%, 69%, and 74% of patients received the planned therapy of both treatment modalities, respectively. Ninety-five percent and 93% of patients in arms 1 and 2, respectively, received the planned two cycles of induction chemotherapy (Table 2). The reasons for not completing induction chemotherapy were progression (four patients), poor health (two patients), death (one patient), treatment-related complications (two patients), and patient refusal (one patient). During the concurrent chemoradiotherapy, 46% of patients in arm 2 and 70% of patients in arm 3 received seven weekly cycles of chemotherapy; 65% of patients in arm 2 and 85% patients in arm 3 completed at least six cycles. Failure to complete at least six weekly cycles of concurrent chemotherapy were attributed to progression (13 patients), poor health (three patients), death (one patient), treatment-related complications (19 patients), patient refusal (two patients), and other reasons (two patients). In arm 3, 67% of patients received the planned two cycles of consolidation chemotherapy. Reasons for not completing consolidation therapy were due to progression (four patients), poor health (five patients), death (four patients), treatment-related complications (11 patients), patient refusal (two patients), and other reasons (four patients).

The percentage of patients who received the scheduled radiotherapy dose was 76% in arm 1, 70% in arm 2%, and 81% in arm 3. The main reasons for receiving incomplete radiotherapy included death (arm 1, n = 1), disease

Table 2. Chemotherapy Administered

	Arm 1 (n = 91) (CT → RT)		Arm 2 (n = 74) (CT → CT + RT)		Arm 3 (n = 92) (RT + CT → CT)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Induction chemotherapy cycles						
0	1	1	1	1		
1	4	4	4	5		
2	86	95	69	93		
Concurrent chemotherapy cycles						
0			14	19	2	2
1			0	0	1	1
2			0	0	0	0
3			1	1	1	1
4			4	5	3	3
5			7	9	7	8
6			14	19	14	15
7			34*	46	64†	70
Postconcurrent chemotherapy cycles						
0					23	25
1					7	8
2					62	67

Abbreviations: CT, chemotherapy; RT, radiotherapy.
*One patient received an extra cycle of chemotherapy for a total of eight cycles.
†Two patients received a total of eight cycles.

progression (arm 1, n = 2; arm 2, n = 7), and patient refusal (arms 1 and 2, n = 3; arm 1, n = 2).

Efficacy

With a median follow-up time of 39.6 months, median survival times of 13.0 months in arm 1, 12.7 months in arm 2, and 16.3 months in arm 3 were obtained. Overall survival rates in arm 1 at 1, 2, and 3 years were 57%, 30%, and 17%; in arm 2, 53%, 25%, and 15%; and in arm 3, 63%, 31%, and 17%.

For arms 1, 2 and 3, the survival curves were similar to those reported with the historical data (Figs 2, 3, and 4). No statistically significant difference in the median overall survival was observed when each of the three treatment arms were individually compared with the historical survival data from arm 2 of RTOG 88-08.

The disease progression rates at 1-year were 54% in arm 1, 46% in arm 2%, and 46% in arm 3. Median progression-free survival was 9.0 months for arm 1, 6.7 months for arm 2, and 8.7 months for arm 3.

Safety

Reported toxicities during the induction chemotherapy phases for arms 1 and 2 are listed in Table 3. Grade 3/4 granulocytopenia occurred in 32% of patients in arm 1 and in 38% of patients in arm 2. Grade 3/4 leukopenia occurred in 18% of patients in arm 1 and in 16% of patients in arm 2. All other toxicities were mild.

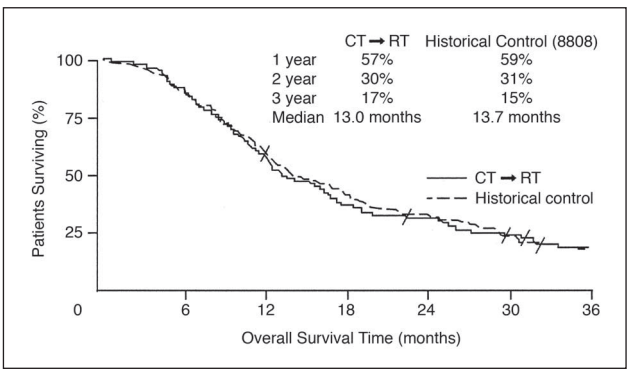

Fig 2. Kaplan-Meier overall survival of patients treated with sequential chemotherapy (CT), paclitaxel, and carboplatin, followed by radiotherapy (arm 1, CT → RT) versus historical control. RT, radiotherapy.

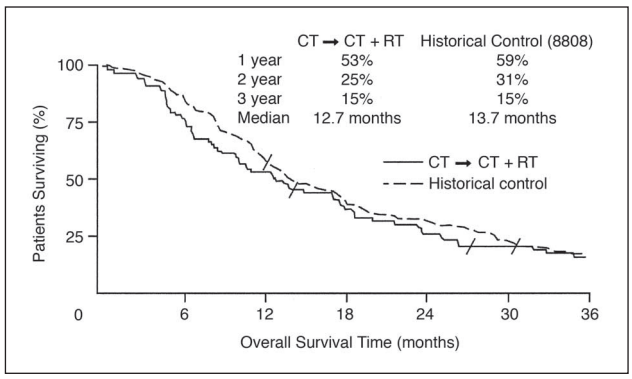

Fig 3. Kaplan-Meier overall survival of patients treated with induction chemotherapy (CT), paclitaxel, and carboplatin, followed by concurrent chemoradiotherapy (arm 2, CT → CT + RT) versus historical control. RT, radiotherapy.

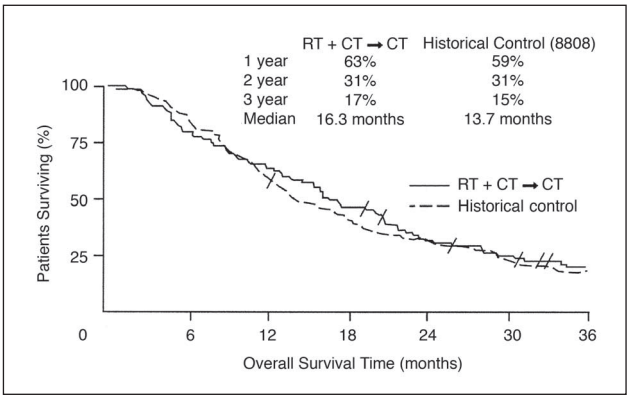

Fig 4. Kaplan-Meier overall survival of patients treated with concurrent chemoradiotherapy followed by consolidation chemotherapy (CT; arm 3, RT + CT → CT) versus historical control. RT, radiotherapy.

Toxicities during and after radiation therapy for all arms are listed in Table 4. Grade 3 and 4 esophagitis occurred in 3% of patients in arm 1, in 19% of patients in arm 2, and in 28% of patients in arm 3. Grade 3/4 granulocytopenia occurred in 16% of patients in arm 2 and 26% of patients in arm 3. Grade 3/4 leukopenia occurred in 2% of patients in arm 1, 31% of patients in arm 2, and 51% of patients in arm 3. Incidence of grade 3/4 thrombocytopenia was 0% for arm 1, 9% in arm 2, and 12% in arm 3. Overall, lung toxicities occurred in 7% of patients in arm 1, 4% of patients in arm 2, and 16% of patients in arm 3. The greater incidence of toxicity observed in arms 2 and 3 as compared with the incidence in arm 1 (Table 4) was not unexpected because both arms included a combined chemotherapy and radiotherapy phase, whereas in arm 1, each modality was given separately.

Three treatment-related deaths were reported within 90 days of study initiation; one patient in arm 2 and two in arm 3. All three deaths were due to infection.

Table 3. Grade 3 and 4 Toxicities Combined-Induction Chemotherapy in Arms 1 and 2

	Arm 1 (n = 91) (CT → RT)		Arm 2 (n = 74) (CT → CT + RT)*	
Toxicity	No. of Patients	%	No. of Patients	%
Anemia	4	4	0	0
Leukopenia	16	18	12	16
Granulocytopenia	29	32	28	38
Thrombocytopenia	4	4	3	4
Hyperglycemia	6	7	5	7
Nausea/vomiting	6	7	6	8
Esophagus	0	0	1	1
Neurologic	3	3	2	3

Abbreviations: CT, chemotherapy; RT, radiotherapy.
*There was one grade 5 toxicity of infection-pneumonia.

DISCUSSION

For patients with locally advanced unresected NSCLC, the combined modality regimen of chemotherapy and radiation is the accepted "standard of care."[8,14] The RTOG 88-08[9] trial compared (1) standard TRT, (2) sequential chemotherapy and TRT, or (3) sequential chemotherapy and hyperfractionated TRT. The best median survival was 13.2 months in the sequential chemoradiotherapy group. However, at the time the present study was developed, 13.7 months was the available median survival for the sequential chemoradiotherapy arm of RTOG 88-08, so this median was used as the historical control.

During the course of the present study, a median survival of 14.6 months was reported for the sequential chemoradiotherapy arm of the Radiation Therapy Oncology group 9410 study.[15] The trial compared three regimens as follows: (1) sequential chemoradiotherapy, (2) concurrent chemoradiotherapy, or (3) concurrent chemotherapy and hyperfractionated TRT.

The results of the present study reveal that all three treatment regimens can be safely administered, with median overall survival times of 13.0 months in arm 1, 12.7 months in arm 2, and 16.3 months in arm 3, comparing favorably with the 13.7 months in RTOG 88-08. Patient populations were slightly different between the present locally advanced multi-modality protocol study (LAMP) and RTOG 88-08. In contrast to the LAMP inclusion criteria, RTOG 88-08 allowed stage II, IIIA, or IIIB patients with a weight loss of less than 5%, and excluded all patients with pleural effusions. As this was a phase II randomized study, statistical comparison among treatment regimens was not performed; however, there was a trend toward a survival benefit for arm 3. Survival results are congruent with RTOG 88-08 and other phase II studies where stage III NSCLC patients were treated with concurrent weekly paclitaxel, carboplatin, and TRT followed by consolidation paclitaxel and carboplatin.[3,18-19,21] Comparisons made to historical survival data from RTOG NSCLC studies using induction chemotherapy followed by radiation therapy indicated that none of the three arms in this study was different than historical controls.[22]

Recently, a number of the newer chemotherapy regimens have been evaluated with concomitant radiotherapy.[23-24] The Cancer and Leukemia Group B (CALGB) combined cisplatin with either gemcitabine, paclitaxel, or vinorelbine, with two cycles given as induction chemotherapy followed by two additional cycles of attenuated doses of the same agents concurrently with TRT.[25] All three treatment agents were deemed safe with similar outcomes, but with different toxicity patterns. An overall median survival of 17 months was reported, similar to the 16.3 months observed in the present trial with concurrent paclitaxel and carboplatin and TRT followed by consolidation

Table 4. Grade 3 and 4 Toxicities Combined, During, and Postradiotherapy (all arms)

Toxicity	Arm 1 (n = 90)* (CT → RT)		Arm 2 (n = 74) (CT → CT + RT)		Arm 3 (n = 92) (RT + CT → CT)†	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Anemia	3	3	5	7	9	10
Cardiac	3	3	2	3	7	8
Esophagitis‡	3	3	14	19	26	28
Granulocytopenia	0	0	12	16	24	26
Hyperglycemia	1	1	3	4	8	9
Leukopenia	2	2	23	31	47	51
Lung	6	7	3	4	15	16
Nausea/vomiting	0	0	6	8	6	7
Neurologic	4	4	5	7	10	11
Thrombocytopenia	0	0	7	9	11	12

Abbreviations: CT, chemotherapy; RT, radiotherapy.
*One patient died prior to receiving radiotherapy and was not included.
†There were two grade 5 toxicities of infection.
‡Kruskall-Wallis test $P < .0001$.

chemotherapy.[25] Based on the published results, the regimen of weekly carboplatin and paclitaxel given concurrently with TRT has become somewhat of a "community standard." To definitively evaluate whether induction full-dose chemotherapy before concurrent chemoradiotherapy is beneficial, the CALGB 39801 study was initiated. Unfortunately, this study failed to show a benefit for the role of induction chemotherapy before the concurrent regimen.[26] This is analogous to what we have reported here in the LAMP trial.

Treatment-related toxicity remains a concern when chemotherapy is combined with TRT. On the sequential, induction/concurrent, and concurrent/consolidation arms of this study, 70%, 69%, and 74% of the patients, respectively, completed the full planned treatment. The occurrence of esophagitis was more frequent on the concurrent/consolidation arm as expected. Similar observations have also been made on the concurrent arm of RTOG 9410, but the incidence of late toxicities such as stricture formation in the esophagus is not substantially increased when both modalities are administered simultaneously.[15] In comparison to RTOG 88-08 arm 2 (sequential), the concurrent/consolidation arm of the LAMP study showed a greater incidence of grade 3 or 4 esophagitis (28% for LAMP *v* 3% for RTOG 88-08 arm 2), and this confirms what has been seen with the concurrent versus sequential regimens. Pulmonary toxicity was also greater in arm 3 in comparison with the other arms of this study.

Other radiation approaches such as hyperfractionated radiation and continuous hyperfractionated accelerated radiotherapy seem to be promising.[27-30] The Eastern Cooperative Oncology Group (ECOG 2597) compared induction chemotherapy with paclitaxel and carboplatin followed by thoracic radiotherapy with hyperfractionated accelerated radiotherapy and reported a higher median survival time in the hyperfractionated accelerated radiotherapy study arm (20.3 months *v* 13.7 months) with an acceptable toxicity profile.[30] Clinical trials are ongoing to evaluate these novel schemes of radiation and advances in radiation therapy, such as three-dimensional conformal therapy and intensity modulated radiation therapy, which may allow the delivery of higher doses of radiation with concurrent chemotherapy.

Although the optimal treatment of locally advanced unresected NSCLC has yet to be defined, the LAMP study demonstrates that concurrent/consolidation treatment appears to be associated with the best outcome though this schedule was associated with greater toxicity. *P* values through 24 months for each arm on LAMP are as follows: arm 1, CT → RT, $P = .4$; arm 2, CT → CT + RT, $P = .8$; and arm 3, RT + CT → CT, $P = .34$. These results are based on very small sample sizes and should be viewed cautiously; however, they are consistent when compared with RTOG 9410. Similar observations have been made in Southwest Oncology Group (SWOG) 9504,[31] where full doses of cisplatin (50 mg/m^2; days 1, 8, 29, and 36) and etoposide (50 mg/m^2; days 1 through 5, and days 29 through 33) were administered with TRT followed by three cycles of docetaxel single agent (75 to 100 mg/m^2). It is also noted that in the LAMP study, concurrent/consolidation therapy yielded the greatest toxicity.

Therefore, although chemoradiotherapy followed by two to three cycles of consolidation chemotherapy seems to be the most efficacious regimen at the moment for the treatment of locally advanced NSCLC, the balance between efficacy and tolerability have to be carefully considered when choosing the appropriate multimodal treatment schedule. Integration of targeted agents into the treatment paradigms and development of newer chemotherapy platforms is being evaluated.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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