A Prospective Phase II Study of Induction Carboplatin and Vinorelbine followed by Concomitant Topotecan and Accelerated Radiotherapy (ART) in Locally Advanced Non-small Cell Lung Cancer (NSCLC)

Samir H. Patel, MD, Munther Ajlouni, MD,* Robert Chapman, MD,† Mei Lu, PhD,‡ Benjamin Movsas, MD,* Jae Ho Kim, MD, PhD**

Background: Survival of locally advanced/unresectable non-small cell lung cancer (NSCLC) has improved with the use of concurrent radiation and chemotherapy over the past decades, but local and distant failure remain high. In addition, a key limiting factor in combining chemotherapy with accelerated radiotherapy (ART) is severe esophagitis. We investigated the toxicity, response rate, and overall survival (OS) with induction carboplatin and vinorelbine followed by concomitant topotecan and ART in patients with locally advanced/unresectable NSCLC.

Methods: In this phase II trial, stage IIIA or IIIB NSCLC patients with a Karnofsky performance score >60 were eligible. Patients received induction carboplatin (area under the curve = 5.5) on days 1 and 22, and vinorelbine (25 mg/m^2) on days 1, 8, 22, and 29. During the concurrent chemoradiation, patients received intravenous topotecan (0.5 mg/m^2) on days 43 to 47, days 57 to 61, and days 71 to 75 before the morning radiotherapy (RT) fraction. RT was administered in an accelerated fashion at 2 Gy per fraction, twice daily for five consecutive days, every other week, to a cumulative dose of 60 Gy during a 5-week period.

Results: Thirty-seven patients were accrued; of these, 35 were evaluable. Overall response rate was 71% (14% complete response, 57% partial response). Six of 35 (17%) patients had stable disease. Four (11%) patients progressed during treatment. At a median follow-up of 45 months for surviving patients, the median survival based on Kaplan–Meier estimates is 17.9 months. OS at 1, 2, and 3 years is 62%, 41%, and 33%, respectively. Actuarial 5-year OS is 21%. The median time to first relapse is 12.2 months (9.1–24.7 months). There were no cases of grade 3 or 4 esophagitis.

Conclusions: This combined-modality regimen yielded encouraging OS rates, with no severe esophagitis. Using four-dimensional RT treatment planning, we plan to further evaluate altered fractionation RT and chemotherapy for this group of patients.

Key Words: Lung cancer, Accelerated radiation, Topotecan.

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Lung cancer is the leading cause of cancer-related death in men and women in the United States, accounting for 162,460 deaths in 2006. Approximately one third of these patients are diagnosed annually with locally advanced/unresectable disease (stages IIIA and IIIB). The "gold standard" treatment strategy has been concurrent chemotherapy with once-daily radiation (RT) to a dose of 60 to 63 Gy.[1–6] Nevertheless, this treatment fails to control disease within the thorax in a significant portion of patients. In addition hematogenous metastasis remains a significant problem with the majority of patients dying of metastatic disease. Although concurrent chemotherapy and RT have made significant advances over sequential chemotherapy followed by RT, the median survival is still around 17 months.[3,5,6] Further intensification of the RT such as via altered fractionation, has shown some promise, but acute toxicity rates especially esophagitis are quite high.[7–9]

Hyperfractionation using 1.2 Gy twice daily has been extensively studied by the Radiation Therapy Oncology Group (RTOG). It was concluded that a dose of 69.6 Gy was optimal.[10] This regimen resulted in a median survival and a 2-year survival rate of 10 months and 20%, respectively. The RTOG further studied hyperfractionation in a randomized phase II trial comparing hyperfractionated RT (69.6 Gy in 58 fractions) with cisplatin chemotherapy versus induction cisplatin and vinblastine followed by cisplatin combined with RT (63 Gy in 34 fractions).[8] This trial showed a significant lengthening of time to in-field progression for the concurrent chemotherapy and hyperfractionated RT arm at the cost of higher rates of esophagitis. Similarly, when this hyperfractionated RT plus chemotherapy regimen was studied in a subsequent randomized trial (RTOG 94-10), this arm was associated with the best local control, but the highest rates of severe esophagitis (50%).[11]

From *Department of Radiation Oncology, †Department of Medical Oncology, and ‡Department of Biostatistics, Henry Ford Hospital, Detroit, Michigan.

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Address for correspondence: Samir H. Patel, Henry Ford Hospital, Department of Radiation Oncology, 2799 W. Grand Blvd., Detroit, MI 48202; E-mail: spatel3@hfhs.org

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At our institution, accelerated RT (ART) was first attempted in locally advanced head and neck cancer on the basis of previous data by Wang et al., yielding dramatic tumor responses and impressive locoregional control.[12,13] The use of accelerated RT is based on the concept that accelerated tumor clonogen repopulation during standard radiotherapy compromises the control rate.[14] The use of accelerated radiotherapy resulting in the reduction of the overall treatment time may result in a therapeutic advantage.[15] We elected to use an every other week regimen of hyperfractionated, accelerated RT and chemotherapy in an attempt to reduce the acute complications—namely, esophagitis—that would occur with a continuous accelerated program, especially when combined with chemotherapy.[16] Despite the interruption, the overall RT treatment time remained relatively short, at 5 weeks.

In 1990, we developed a phase II trial examining a treatment regimen for locally advanced (stages IIIA and IIIB) carcinoma of the lung that used ART therapy consisting of 55.6 Gy in 30 fractions (1.8 Gy bid for five consecutive days, given every other week).[17] Concurrent chemotherapy included cisplatin (10 mg/m^2), vinblastine (4 mg/m^2), 6-thioguanine (40 mg, twice daily), and 5-fluorouracil (400 mg/m^2, continuous infusion), and consolidation chemotherapy consisted of two cycles of cisplatin (120 mg/m^2) and vinblastine (4 mg/m^2). The trial showed promising results: a 63% response rate, with a median survival of 17.5 months. Furthermore, the acute grade 3 or 4 esophagitis rate was only 2.8%. Because of the poor tolerance to consolidation chemotherapy, we elected to deliver two cycles of chemotherapy upfront in this trial. We also decided to use cisplatin and vinorelbine as induction chemotherapy because of data suggesting improved activity of cisplatin and vinorelbine over cisplatin alone.[18] Because of the low toxicity encountered in the first trial, we elected to increase the dose per fraction to 2.0 Gy, giving a total dose of 60 Gy in 5 weeks. For the chemotherapy used during the ART portion of the treatment, we chose to use topotecan concurrently. The decision to add topotecan to this regimen was the result of data generated in our laboratory indicating that this drug has significant RT-enhancing properties.[19] In our preclinical studies, topotecan caused a dose-dependent reduction in cell survival after irradiation in Hela S-3 cells and in murine fibrosarcoma. Moreover, phase I and II trials have shown efficacy in the treatment of non-small cell lung cancer (NSCLC).[20,21] A phase I trial has shown that the optimal dose of 0.5 mg/m^2 during thoracic irradiation can be safely delivered, while avoiding hematologic and gastrointestinal toxicity.[21] Because of the promising results of our previous phase II trial, we decided to study the use of ART in conjunction with novel chemotherapeutic agents to further improve efficacy while minimizing toxicity in locally advanced NSCLC patients.

PATIENTS AND METHODS

Patient Eligibility and Statistics

This was a phase II trial with a two-stage clinical design with a planned sample size of 40 patients and an expected response rate of 85%, representing an absolute improvement of 20% over our previous phase II trial.[17] Initially, 20 patients were enrolled, and a planned interim analysis revealed 17 patients achieving objective responses, which required another 20 patients to be enrolled to the second stage. On a second interim analysis, 10 of the 37 patients failed to achieve objective responses and because the study goal response rate could not be met, an early-stopping rule required the trial to be stopped early. Therefore, between June 1999 and December 2003, 37 patients with locally advanced, unresectable NSCLC were enrolled on an institutional review board approved protocol using induction chemotherapy followed by combined chemotherapy and ART. Eligibility requirements included having histologically or cytologically proven NSCLC with unresectable stage IIIA or IIIB disease as demonstrated on computed tomography (CT) scan of the chest and upper abdomen. In addition, a 24-hour creatinine clearance of 60 ml/min or greater, white blood count equal to 4000 or greater, and a platelet count greater than 100,000 were required. Patients were required to be 18 years of age, capable and willing to sign an informed consent form, and have a Karnofsky performance score (KPS) $\geq$ 60. Patients with prior diagnosis of a second malignancy, except for basal cell carcinoma of the skin, were ineligible. Moreover, those previously treated with RT or chemotherapy were ineligible.

Before registration, a pretreatment evaluation was done consisting of a complete history and physical, complete blood count, differential, and platelet count, 24-hour urine for creatinine clearance or a calculated creatinine clearance and screening profile of liver function and serum electrolytes. Radiologic imaging included CT scan of the chest and upper abdomen. A CT scan of the brain if neurologic abnormalities were present on history or on careful neurologic exam, and radionuclide scans of the bone were done if clinically indicated. Bronchoscopy was performed in the majority of cases, but this was not required.

Of the 37 patients enrolled, 35 patients were evaluable. One patient completed the induction phase of the protocol but was taken off the protocol because of persistent thrombocytopenia. A second patient completed the planned treatment course but was lost to follow-up. The patient characteristics are listed in Table 1.

Treatment Program

The induction phase of treatment consisted of carboplatin (area under the curve = 5.5) on days 1 and 22, administered by intravenous infusion for 30 minutes, and vinorelbine (25 mg/m^2) on days 1, 8, 22, and 29, administered by intravenous infusion for 5 to 10 minutes. Dose adjustments were based on blood counts, renal function, hepatic function, and/or neurologic toxicity. The combined chemotherapy–RT phase began on day 43. ART was delivered at 2 Gy per fraction, twice a day, for a total dose of 60 Gy on days 43 to 47, days 57 to 61, and days 71 to 75, including two planned breaks during weeks 8 and 10. Each day, the treatment fractions were separated by at least 6 hours. Topotecan (0.5 mg/m^2, administered intravenously for 30 to 60 minutes) was administered 1 to 2 hours before the first RT treatment daily on days 43 to 47, days 57 to 61, and days 71 to 75.

RT was planned using a CT simulation with patients in the supine position. An alpha cradle or approved alternate

TABLE 1. Patient Characteristics

	Number	Percent
Age		
≤60	6	17
>60	29	83
Gender		
Male	23	66
Female	12	34
Weight loss percentage		
≤5	28	80
>5–10	3	9
>10	4	11
KPS		
60–70	7	20
80–100	28	80
Type		
Squamous	12	34
Adenocarcinoma	11	32
Non-small cell	12	34
AJCC stage		
IIIA	25	74
IIIB	10	26
AJCC TNM		
T1N2	8	23
T2N2	12	34
T3N2	5	14
T4N0	2	6
T4N2	5	14
T2N3	1	3
T3N3	1	3
TxN3	1	3

KPS, Karnofsky performance status; AJCC, American Joint Committee on Cancer; TNM, tumor, node, metastasis.

immobilization was required. Intravenous contrast during the planning CT was optional, provided a diagnostic chest CT with contrast was done. Three-dimensional conformal RT was used with megavoltage equipment with photon energies ≥6 MeV required. Secondary blocking was used in all cases with cerrobend blocks or multileaf collimation. The initial treatment volume was a clinical target volume (CTV) consisting of the gross tumor volume (GTV) + 1.5 to 2 cm to encompass primary echelon lymph nodes. Furthermore the GTV included abnormally enlarged lymph nodes measuring >1.0 cm in the short axis. The initial planning target volume provided a minimum margin of 1.0 cm around the CTV, with an additional margin if deemed necessary for respiratory motion, as measured by fluoroscopy. This initial PTV was treated to a minimum dose of 44 Gy at 2 Gy per fraction. This was followed by a boost of 16 Gy at 2 Gy per fraction to the GTV. The initial field was treated twice a day (morning and afternoon/evening) during weeks 7 and 9 and on the first day of week 11. On the remaining 4 days of week 11, the boost volume was treated in the morning and afternoon/evening. Maximum doses to critical normal tissues were 25 Gy to peripheral lung not within target volume, 42 Gy to the spinal cord, 45 Gy (if feasible) to the esophagus, and 35 Gy to <50% of the heart.

Treatment Evaluation

Four to six weeks after completion of treatment, patients underwent CT scanning of the chest and upper abdomen to evaluate their responses, using the World Health Organization response criteria, which was the primary endpoint. Partial response was defined as greater than 50% decrease in the product of the longest perpendicular diameters of each measurable lesion. Complete response was defined as the absence of clinical, laboratory, and radiographic evidence of disease. The definition of progression of disease includes the appearance of new lesions or the increase of measurable disease. Follow-up visits were conducted every 3 months for the first 2 years, then every 6 months thereafter. Before each follow-up visit, a CT scan of the chest and upper abdomen was obtained. Acute and late toxicity were scored using the RTOG/European Organisation for Research and Treatment of Cancer toxicity criteria. Survival was calculated from the time of registration on the study until death, using the Kaplan–Meier actuarial method.

RESULTS

Toxicity

The most common acute toxicity was hematologic, with grade 3 or 4 leukopenia occurring in 74% of patients and grade 3 or 4 anemia occurring in 17% of patients. The majority of patients experienced hematologic toxicity during the induction phase of the treatment. This resulted in 20% of patients receiving a delay or reduction in dose of chemotherapy. The hematologic toxicity was reversible in the vast majority of patients, such that no patient had the two cycles of induction chemotherapy omitted, and only one patient received one of the two cycles of induction chemotherapy. Five patients experienced an infectious process, which included postobstructive pneumonia, bacterial sepsis, perianal fungal infection, and mediport infection. The most common acute toxicity during the concurrent topotecan and ART was esophagitis. All cases of esophagitis were grade 1 or 2, which occurred in 19 (54%) patients. All 35 evaluable patients were able to complete the concurrent phase of treatment without any interruptions. One patient did not receive the boost-RT portion because of the diagnosis of metastatic brain disease.

The most common late toxicity was cough, which was all grade 1 or 2, and occurred in 11 (31%) patients. Two patients were diagnosed with grade 3 or 4 pneumonitis; the patient with grade 4 pneumonitis was also diagnosed with a pulmonary embolus. No unusual late toxicities were noted. Table 2 summarizes the acute and late toxicities.

Response/Survival

A total of 25 (71%) patients had a partial or complete response to the therapy (Table 3). Of the five patients who had a complete response, only two patients lived longer than one year. Furthermore, it was interesting to note that two of the nine patients living longer than 3 years were deemed nonresponders and that five of the nine patients were partial

TABLE 2. Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Acute					
Anemia	9	15	8	1	17
Leukopenia	5	5	14	12	74
Thrombocytopenia	11	4	2	0	6
Esophagitis	13	6	0	0	0
Mucosal	1	0	0	0	0
Nausea/vomiting	12	3	2	0	6
Cough	12	3	0	0	0
Infection	0	4	1	0	3
Renal	0	0	0	0	0
Hearing loss	0	1	1	0	3
Late					
Dyspnea	1	2	1	0	3
Cough	8	3	0	0	0
Radiation pneumonitis	0	2	1	1	6
Hearing	0	0	0	0	0
Renal	0	0	0	0	0
Esophagus	1	1	0	0	0

responders. No association was found between treatment response and survival beyond 3 years ($p = 0.92$). The Kaplan–Meier 1-year, 2-year, 3-year, and actuarial 5-year overall survival (OS) were 63%, 40%, 30%, and 17%, respectively, as shown in Figure 1. The median OS was 17.9 months (95% confidence interval: 10–30.7 months), with a median follow-up of 45 months. Five patients lived longer than 4.5 years, with four of these long-term survivors still alive at this time. A total of seven baseline covariates, including stage (IIIA versus IIIB), tumor histology, age, gender, Karnofsky score, the maximum lesion size greater than the observed median (5.3 cm) and weight loss >5%, were included in the analysis. Results showed that the lesion size had a trend towards predicting ($p < 0.10$) survival on univariate analysis. On multivariate analysis, the one variable retained was maximum lesion size ($p = 0.009$). Patients with a maximum lesion size >5.3 cm had a fourfold risk (hazards ratio = 4.43; confidence interval = 1.84–10.64) of death. Figure 2 shows the Kaplan–Meier curve stratified for lesion size.

Patterns of Failure

The median time to first relapse was 12.2 months (9.1–24.7 months). Some type of failure was seen in 24 of the 35 patients (69%), with the most common first relapse being local failure. Patients living longer than 3 years did not show a specific pattern of failure: three patients failed locally, one patient failed distantly, two patients failed locally and distantly, and three patients had stable disease. Table 4 summarizes the patterns of failure.

TABLE 3. Response

Response	Number	Percent
Complete response	5	14
Partial response	20	57
No response	6	17
Progression	4	11
Any response	25	71

DISCUSSION

This trial was designed to build on the previous trial we had performed in the phase II setting.[17] The prior trial consisted of 35 patients and used ART to a total dose of 55.6 Gy at 1.8 Gy, twice a day. Patients received concurrent chemotherapy consisting of cisplatin, vinblastine, 6-thioguanine, and 5-flurouracil, and then consolidation chemotherapy consisting of cisplatin and vinblastine. Because of the poor compliance and tolerance to the consolidation chemotherapy, our current trial implemented two cycles of chemotherapy upfront. Our current trial was able to deliver the induction chemotherapy with good compliance and minimal dose reductions, and it also achieved an escalation in the RT dose without increasing the toxicity rates. Compared with the previous trial, the overall response rate was 71% versus 63%. Furthermore, the median survival was similar at 17.9 months versus 17.5 months, though the 3-year survival was higher at 30% versus 20% in the previous trial. Similar toxicity profiles were noted, with minimal grade 3 or 4 esophagitis seen. Interestingly, our previous trial had an increased distant failure rate of 40% compared with our current trial rate of 23%, which may have been attributable to the poor tolerance to consolidation chemotherapy in the prior trial.

One of the major problems associated with the use of altered fractionation with chemotherapy is severe esophagitis. It has been shown, in an analysis of predictors for esophagitis by Werner-Wasik et al.,[9] that the maximum acute esophagitis grade is associated with the use of chemotherapy and twice-daily RT. Many trials using concurrent chemotherapy with altered fractionation have shown increased grade 3 and 4

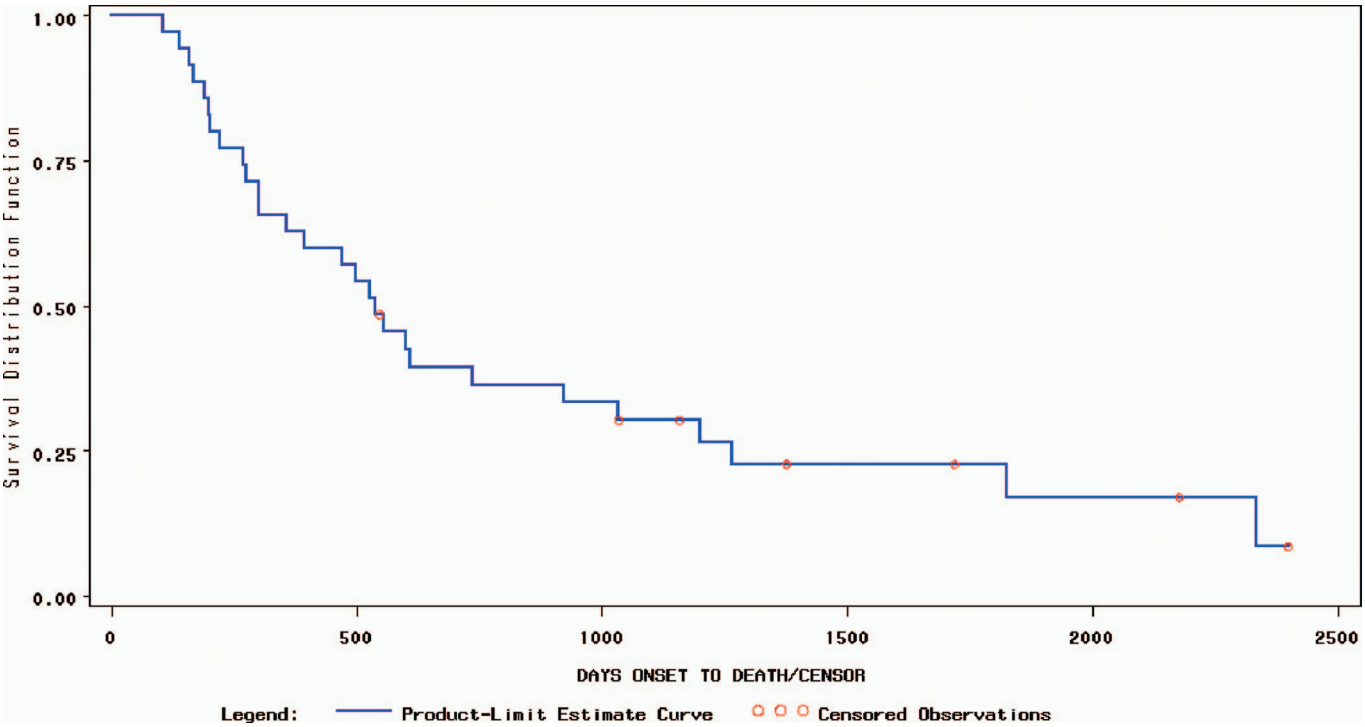

FIGURE 1. Overall survival.

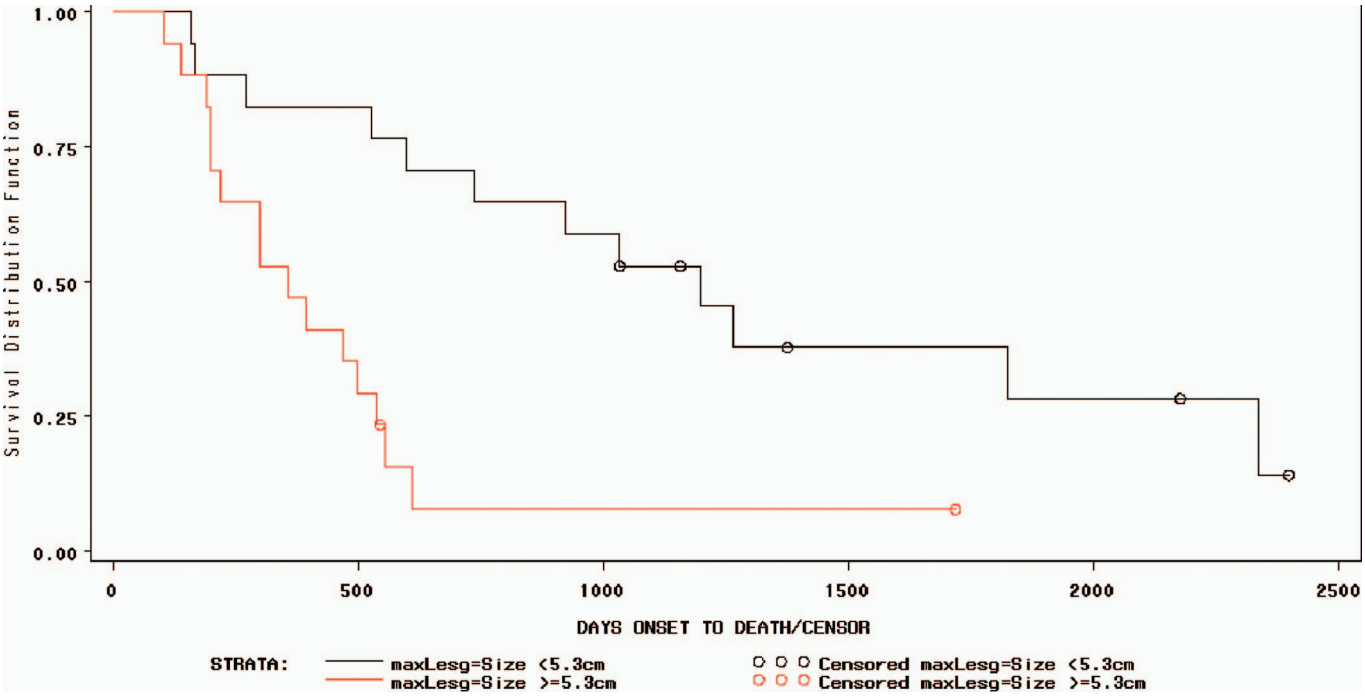

FIGURE 2. The effect of lesion size (<5.3 cm in *black* versus ≥5.3 in *red*) on survival.

esophagitis rates >30%[6,8,16] Yet, our regimen of ART allowed us to deliver 60 Gy in 5 weeks, with essentially no severe esophagitis.

At the same time, regarding survival, our median survival of 17.9 months was comparable with the median survival of 17.0 months reported for the concurrent chemotherapy and once-daily RT arm in RTOG 94-10 and the median survival of 16.5 months reported for the concurrent chemotherapy and RT arm in the Japanese randomized trial.[5,6] The 5-year survival rate was similarly promising, at 20%. Of note,

TABLE 4. Patterns of Failure[a]

	Number	Percent
Local failure only	10	29
Distant failure only	8	23
Local and distant failure	6	17
Stable	4	11
Progression	4	11
Unknown	3	9

[a] Sites of initial relapse are reported.

the Japanese trial included a planned 2-week treatment break, whereas our trial used two 1-week breaks. Although treatment breaks are not considered optimal because of the possibility of accelerated repopulation, it is critical to keep in mind that our regimen delivered 60 Gy in only 5 weeks. From a radiobiological perspective, this is a more intensive RT dose than 60 to 63 Gy in 6 to 7 weeks (using once-daily RT).

On multivariate analysis, it was not surprising to find that lesion size had a significant effect on survival, because this factor reflects tumor volume. Local failure was a component of initial treatment failure in 16 patients (46%), indicating a need for more effective locoregional control. We feel that treatment intensification should include escalating the dose of RT. One possibility is to continue ART to a dose above 60 Gy, because we were able to minimize our dose-limiting toxicities. A recent phase I dose-escalation study reported by Marks et al.[22] used induction carboplatin/paclitaxel or carboplatin/vinorelbine and then accelerated hyperfractionated conformal RT alone; in that study, well-selected patients were able to tolerate a dose of approximately 80 Gy using 1.25 to 1.6 Gy, twice daily. RTOG is currently developing an RT dose-escalation trial in stage III NSCLC, comparing 60 Gy with concurrent chemotherapy against 74 Gy with concurrent chemotherapy. Another option for RT dose intensification may be stereotactic radiotherapy. There is emerging evidence for excellent local control of early-stage inoperable lung cancers.[23,24] A fractionated stereotactic RT boost may be useful for dose escalation while limiting the dose to neighboring organs at risk.[25] This could potentially be targeted at areas of bulky disease during the planned ART breaks, thereby avoiding the potential concern regarding accelerated repopulation. Clearly, the optimal stereotactic dose-fractionation scheme needs to be carefully studied for central lesions, to avoid undue late toxicity.[26] We have experienced treating central lesions with stereotactic RT (using four doses up to 12 Gy) with no evidence of toxicity, with a median follow-up approaching 1 year (Munther Ajlouni, personal communication, 2007). With further intensification, a dosimetric analysis of the esophagus and lung would yield valuable information regarding the role of ART.

Our current trial does not show a marked improvement in response over our previous trial, but both trials have shown minimal grade III/IV esophagitis while maintaining a response and survival rate consistent with the current literature, as mentioned. Two variables, ART and topotecan, are responsible for these findings, but it is unclear whether these findings are secondary to ART alone, topotecan alone, or a combination of both. The common denominator in both of our phase II trials is the use of ART, and we feel that this RT scheme is mainly responsible for the observed esophagitis rates. Limited phase I data have shown grade 3 esophagitis occurring in one of six patients treated with topotecan and conventional external-beam RT (60 Gy at 2 Gy per day).[21] Although topotecan has shown modest activity in advanced NSCLC, and our laboratory data suggest a significant RT-enhancing effect, more clinical data are needed regarding its efficacy in the locally advanced NSCLC setting.[27,28] Newer agents are being evaluated to further improve the results. One example is the use of RSR13 in a phase II trial, reported by Choy et al.,[29] using induction carboplatin and paclitaxel and then RT (64 Gy in 32 fractions) with RSR13. They report a median survival of 20.6 months. Studies are now emerging testing the role of novel biologic strategies, such as tyrosine kinase inhibitors, as part of the multimodality treatment of patients with stage III NSCLC (e.g., the RTOG phase II study with cetuximab[30]).

Although the number of patients in this prospective phase II trial is relatively small, we are encouraged by the promising survival rates observed, particularly in the absence of severe esophagitis in both of our phase II trials employing ART with chemotherapy. These experiences suggest that ART warrants further study with treatment intensification consisting of RT dose escalation in conjunction with novel systemic agents.

REFERENCES

1. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210–1215.
2. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995;87:198–205.
3. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524–530.
4. Le Chevalier T, Brisgand D, Douillard JY, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994;12:360–367.
5. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
6. Curran WJ, Scott CB, Langer CJ, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III non small cell lung cancer: RTOG 9410. *Proc Annu Meet Am Assoc Cancer Res* 2003;22:A2499.
7. Saunders MI, Dische S. Continuous, hyperfractionated, accelerated radiotherapy (CHART) in non-small cell carcinoma of the bronchus. *Int J Radiat Oncol Biol Phys* 1990;19:1211–1215.
8. Komaki R, Seiferheld W, Ettinger D, et al. Randomized phase II chemotherapy and radiotherapy trial for patients with locally advanced inoperable non-small-cell lung cancer: long-term follow-up of RTOG 92-04. *Int J Radiat Oncol Biol Phys* 2002;53:548–557.
9. Werner-Wasik M, Pequignot E, Leeper D, et al. Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: a multivariate analysis of patients with lung cancer treated with nonoperative therapy. *Int J Radiat Oncol Biol Phys* 2000;48:689–696.

10. Cox JD, Azarnia N, Byhardt RW, et al. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. *J Clin Oncol* 1990;8:1543–1555.
11. Komaki R, Seiferheld W, Curran W, et al. Sequential vs. concurrent chemotherapy and radiation therapy for inoperable non-small cell lung cancer (NSCLC): analysis of failures in a phase III study (RTOG 94-10). *Int J Radiat Oncol Biol Phys* 2000;48(3 suppl):113.
12. Dragovic J, Doyle TJ, Tilchen EJ, et al. Accelerated fractionation radiotherapy and concomitant chemotherapy in patients with stage IV inoperable head and neck cancer. *Cancer* 1995;76:1655–1661.
13. Wang CC, Blitzer PH, Suit HD. Twice-a-day radiation therapy for cancer of the head and neck. *Cancer* 1985;55:2100–2104.
14. Withers HR, Flow BL, Huchton JI, et al. Effect of dose fractionation on early and late skin responses to gamma-rays and neutrons. *Int J Radiat Oncol Biol Phys* 1977;3:227–233.
15. Machtay M, Hsu C, Komaki R, et al. Effect of overall treatment time on outcomes after concurrent chemoradiation for locally advanced non-small-cell lung carcinoma: analysis of the Radiation Therapy Oncology Group (RTOG) experience. *Int J Radiat Oncol Biol Phys* 2005;63:667–671.
16. Reguart N, Vinolas N, Casas F, et al. Integrating concurrent navelbine and cisplatin to hyperfractionated radiotherapy in locally advanced non-small cell lung cancer patients treated with induction and consolidation chemotherapy: feasibility and activity results. *Lung Cancer* 2004; 45:67–75.
17. Ajlouni M, Chapman R, Kim JH. Accelerated-interrupted radiation therapy given concurrently with chemotherapy for locally advanced non-small cell lung cancer. *Cancer J Sci Am* 1996;2:314–320.
18. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol* 1998;16:2459–2465.
19. Kim JH, Kim SH, Kolozsvary A, et al. Potentiation of radiation response in human carcinoma cells in vitro and murine fibrosarcoma in vivo by topotecan, an inhibitor of DNA topoisomerase I. *Int J Radiat Oncol Biol Phys* 1992;22:515–518.
20. Perez-Soler R, Fossella FV, Glisson BS, et al. Phase II study of topotecan in patients with advanced non-small-cell lung cancer previously untreated with chemotherapy. *J Clin Oncol* 1996;14:503–513.
21. Graham MV, Jahanzeb M, Dresler CM, et al. Results of a trial with topotecan dose escalation and concurrent thoracic radiation therapy for locally advanced, inoperable nonsmall cell lung cancer. *Int J Radiat Oncol Biol Phys* 1996;36:1215–1220.
22. Marks LB, Garst J, Socinski MA, et al. Carboplatin/paclitaxel or carboplatin/vinorelbine followed by accelerated hyperfractionated conformal radiation therapy: report of a prospective phase I dose escalation trial from the Carolina Conformal Therapy Consortium. *J Clin Oncol* 2004; 22:4329–4340.
23. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004;101:1623–1631.
24. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys* 2005;63:1010–1015.
25. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003;124:1946–1955.
26. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–4839.
27. Schiller JH. Future role of topotecan in the treatment of lung cancer. *Oncology* 2001;61(suppl 1):55–59.
28. Perez-Soler R. Topotecan in the treatment of non-small cell lung cancer. *Semin Oncol* 1997;24:S20-34–S20-41.
29. Choy H, Nabid A, Stea B, et al. Phase II multicenter study of induction chemotherapy followed by concurrent efaproxiral (RSR13) and thoracic radiotherapy for patients with locally advanced non-small-cell lung cancer. *J Clin Oncol* 2005;23:5918–5928.
30. Werner-Wasik M, Swann S, Curran W, et al. A phase II study of cetuximab (C225) in combination with chemoradiation (CRT) in patients (PTS) with stage IIIA/B non-small cell lung cancer (NSCLC): an interim overall toxicity report of the RTOG 0324 trial. *J Clin Oncol* 2005;23(suppl):7135.

