REPORTS

Improved Survival in Stage III Non-Small-Cell Lung Cancer: Seven-Year Follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial

*Robert O. Dillman, James Herndon, Stephen L. Seagren, Walter L. Eaton, Jr., Mark R. Green**

Background: **For many years, high-dose radiation therapy was the standard treatment for patients with locally or regionally advanced non-small-cell lung cancer (NSCLC), despite a 5-year survival rate of only 3%-10% following such therapy. From May 1984 through May 1987, the Cancer and Leukemia Group B (CALGB) conducted a randomized trial that showed that induction chemotherapy before radiation therapy improved survival during the first 3 years of follow-up.** ***Purpose:*** **This report provides data for 7 years of follow-up of patients enrolled in the CALGB trial.** ***Methods:*** **The patient population consisted of individuals who had clinical or surgical stage III, histologically documented NSCLC; a CALGB performance status of 0-1; less than 5% loss of body weight in the 3 months preceding diagnosis; and radiographically visible disease. Patients were randomly assigned to receive either 1) cisplatin (100 mg/m^2 body surface area intravenously on days 1 and 29) and vinblastine (5 mg/m^2 body surface area intravenously weekly on days 1, 8, 15, 22, and 29) followed by radiation therapy with 6000 cGy given in 30 fractions beginning on day 50 (CT-RT group) or 2) radiation therapy with 6000 cGy alone beginning on day 1 (RT group) for a maximum duration of 6-7 weeks. Patients were evaluated for tumor regression if they had measurable or evaluable disease and were monitored for toxic effects, disease progression, and date of death.** ***Results:*** **There were 78 eligible patients randomly assigned to the CT-RT group and 77 randomly assigned to the RT group. Both groups were similar in terms of sex, age, histologic cell type, performance status, substage of disease, and whether staging had been clinical or surgical. All patients had measurable or evaluable disease at the time of random assignment to treatment groups. Both groups received a similar quantity and quality of radiation therapy. As previously reported, the rate of tumor response, as determined radiographically, was 56% for the CT-RT group and 43% for the RT group (P = .092). After more than 7 years of follow-up, the median survival remains greater for the CT-RT group (13.7 months) than for the RT group (9.6 months) (P = .012) as ascertained by the logrank test (two-sided). The percentages of patients surviving after years 1 through 7 were 54, 26, 24, 19, 17, 13, and 13 for the CT-RT group and 40, 13, 10, 7, 6, 6, and 6 for the RT group.** ***Conclusions:*** **Long-term follow-up confirms that patients with stage III NSCLC who receive 5 weeks of chemotherapy with cisplatin and vinblastine before radiation therapy have a 4.1-month increase in median survival. The use of sequential chemotherapy–radiotherapy increases the projected proportion of 5-year survivors by a factor of 2.8 compared with that of radiotherapy alone. However, inasmuch as 80%-85% of such patients still die within 5 years and because treatment failure occurs both in the irradiated field and at distant sites in patients receiving either sequential chemotherapy–radiotherapy or radiotherapy alone, the need for further improvements in both the local and systemic treatment of this disease persists. [J Natl Cancer Inst 1996;88:1210-5]**

The Cancer and Leukemia Group B (CALGB) conducted a randomized phase III trial (CALGB 8433) from May 1984 through May 1987 in patients with stage III non-small-cell lung cancer (NSCLC). In this trial, they compared the current standard treatment, a relatively high dose of external-beam radiation therapy, with a new treatment plan that included 2 months of chemotherapy with cisplatin and vinblastine followed by the same radiation therapy. The initial results of this trial were encouraging (*1*) and have been published (*2*). The publication (*2*) included follow-up data for the first 3 years from initiation of treatment. The reports of this trial changed how many practicing clinicians treat this stage of lung cancer and have rekindled enthusiasm for the systemic treatment of lung cancer. Recently, an intergroup trial (*3*) initiated by the Radiation Therapy Oncology Group (RTOG), in which two of the study arms were identical to those used in CALGB 8433, confirmed the initial survival advantage conveyed by this sequential, multimodality approach. Many physicians, however, have remained skeptical that such a survival advantage could be retained beyond the first 2-3 years following such treatment.

In this report, we present long-term survival results based on a median fol-

**Affiliations of authors:* R. O. Dillman, Hoag Cancer Center, Newport Beach, CA; S. L. Seagren, M. R. Green, University of California, San Diego; J. Herndon, Duke University Medical Center, Durham, NC; W. L. Eaton, Jr., Dartmouth Medical School, Hanover, NH.

Correspondence to: Robert O. Dillman, M.D., Hoag Cancer Center, 301 Newport Blvd., Newport Beach, CA 92663.

See "Notes" section following "References."

low-up of more than 8 years for the patients enrolled in the CALGB 8433 trial.

Patients and Methods

Patient Eligibility

Eligibility requirements for accrual to this trial were previously detailed (*2*). Before patients could be randomly assigned to one of the two treatment arms, their eligibility was determined by a medical oncologist and a radiation oncologist. Written informed consent was obtained from each patient, and the treatment protocol was approved by the specific local review boards of participating institutions in accord with, when appropriate, assurances filed with and approved by the U.S. Department of Health and Human Services. Only patients with a histologic diagnosis of NSCLC (squamous cell carcinoma, adenocarcinoma, or large-cell anaplastic carcinoma) were eligible. Patients had to have clinical or surgical T3 or N2 and M0, stage III disease based on the staging system in use at the time the trial was initiated (*4*). These patients would be considered to have stage IIIA or IIIB disease by use of the current lung cancer staging system (*5*); however, patients with involvement of supraclavicular or scalene lymph nodes (or both) or cytologically malignant pleural effusions were excluded from CALGB 8433 because such metastases are associated with a poor prognosis. Patients who had undergone surgical debulking of tumor, such that no disease was visible radiographically, were not eligible. Radiologic assessment included chest x ray, ^{99}technetium bone scan, and computerized axial tomography of the chest and upper abdomen, including the adrenal glands and kidneys. Brain imaging was required only if there were symptoms or signs suggestive of brain metastases. Patients had to have "measurable disease" (i.e., a tumor mass measurable in two perpendicular diameters) or "evaluable disease" (i.e., a radiographically visible tumor lesion that could not be measured accurately in two dimensions). Pleural effusions were not considered measurable or evaluable. Only patients with a good performance status were eligible (CALGB performance level of 0 or 1); i.e., patients were able to carry out normal daily activities, including light work, but limitations in vigorous physical activity were allowed. Patients were ineligible if they had lost more than 5% of their body weight during the 3 months before diagnosis or if they had received previous chemotherapy or radiation therapy. At the time of study entry, patients had to have had a hematocrit greater than 30%; a granulocyte count higher than 3500/μL; a platelet count higher than 100 000/μL; and levels of serum blood urea nitrogen, creatinine, and bilirubin less than 1.5 times the upper range for normal laboratory values.

Treatment

The safety and efficacy of the chemotherapeutic agents used in this study have been established previously in a randomized phase II trial conducted by the CALGB (*6*). The chemotherapy in the present trial included vinblastine (5 mg/m^2 body surface area), which was given for 5 weeks as an intravenous bolus on days 1, 8, 15, 22, and 29, and cisplatin (100 mg/m^2 body surface area), which was given monthly intravenously over a 30- to 60-minute period on days 1 and 29. Exactly the same dose and schedule of these two agents were used subsequently in one arm of the confirmatory randomized trial initiated by the RTOG (*3*). The protocol stipulated specific modifications of drug dosage on the basis of blood cell counts and tests of renal and hepatic functions on the day of therapy. Neither drug was given until day 36 if either drug could not be given on day 29.

The radiation therapy given in this study was based on the results of previous trials conducted by the RTOG (*7*). Radiotherapy was started within 5 days after enrollment in the protocol for patients randomly assigned to receive only radiation therapy (RT group). Radiotherapy began on day 50 (2-3 weeks after completion of chemotherapy) for patients assigned to sequential chemotherapy–radiation therapy (CT-RT group). To ensure that radiotherapy could start on day 50 as planned, no chemotherapy was given after day 36. The area of cancer involvement in the lung was treated with external-beam photon radiation therapy as previously detailed (*2*). The dose received by the entire tumor was 6000 cGy delivered in twenty 200-cGy fractions over a 4-week period to the original tumor volume and ten 200-cGy fractions over a 2-week period to the boost volume (surrounding the tumor for which no definite assessment could be made). Thus, the entire radiation treatment was delivered over a 6- to 7-week interval for both treatment groups.

Statistical Analysis

The manner in which this trial was monitored, how data were analyzed, and the quality-assurance assessment of the delivery of radiation therapy were detailed earlier (*2*). CALGB 8433 was a prospective, randomized trial of two different treatment arms: CT-RT and RT. The only stratification of subjects prior to random assignment to treatment group was by histologic type of tumor. Pearson's chi-squared test or the corresponding exact test was used to determine the comparability of the patient populations and the response rates observed in patients in each treatment arm. The degree of tumor regression was assessed after the completion of chemotherapy for the CT-RT group. Tumor response was also determined 1 month after radiation therapy was completed in both groups and then every 2 months thereafter by use of standard criteria as previously described (*2*).

Our major objective in CALGB 8433 was to compare overall survival in the two treatment groups. Survival was calculated from the date of enrollment into the protocol until the date of death or the last date for which follow-up information was available. Treatment failure-free survival was calculated from the date of study entry to the date of disease progression, date of relapse after a previous response, or date of death from any cause. All survival curves were generated by the Kaplan–Meier life-table method (*8*). Survival of patients in the two treatment groups was compared with the use of the logrank test for censored data (*9*) or a Cox model to control for prognostic factors (*10*). Two-tailed tests were used for all statistical comparisons.

Results

Patient accrual to CALGB 8433 took place from May 1984 through May 1987. Twenty-five patients (14%) were ineligible and were excluded from the final analysis; these 25 patients included seven patients from each treatment group who were withdrawn before therapy began and 11 patients who were excluded after subsequent analysis. The latter 11 included four patients in the CT-RT arm (two who actually had metastatic disease at the time of study entry, one who had a performance status of 2, and one who had no residual tumor after surgery). The other seven patients who were subsequently deemed ineligible were randomly assigned to the RT group; four of these patients had metastatic disease, one had a performance status of 2, and two had only stage II disease. There were two patients with a performance status of 2 (one in each treatment arm); these patients were prospectively declared eligible for the trial because of the existence of reversible medical problems unrelated to their cancer, which were limiting their physical activity.

The characteristics of the 155 eligible patients were previously described (*2*). There were no statistically significant differences between the two treatment groups in terms of sex, age, histologic cell type, or performance status. A subsequent retrospective radiographic analysis for stage did not suggest an imbalance between the two treatment arms in the distribution of patients with stage IIIA or stage IIIB disease (*11*). The disease in approximately half of the patients in each group was staged by mediastinoscopy or thoracotomy. None of the patients had surgical resection of residual disease after the assigned treatment.

Patient entry to CALGB 8433 had been closed for more than 7 years at the time of this analysis, and the key end point, death, is known to have occurred in 90% of the study population. Follow-up in this trial has been excellent, as exemplified by the fact that only five patients (three in the CT-RT arm and two in the RT arm) were censored from the data at less than 4 years of follow-up. Statistically significant differences have persisted between the two groups in overall survival (Fig. 1) and in treatment failure-free survival (Fig. 2). The overall differences in

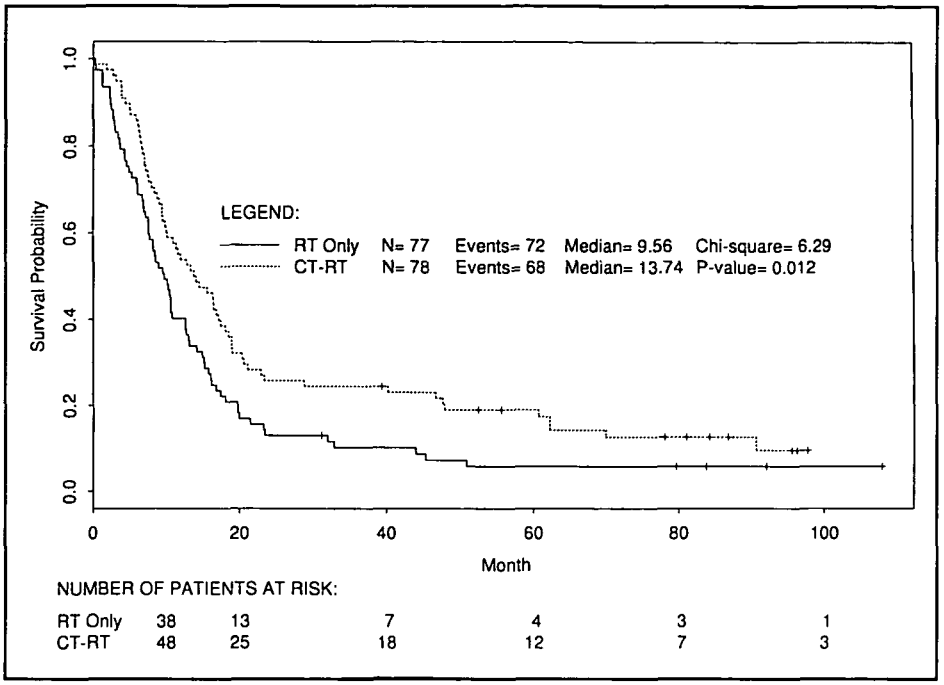

Fig. 1. Overall survival of patients with stage III non-small-cell lung cancer after sequential chemotherapy–radiation therapy (CT-RT) compared with that of patients after radiation therapy alone (RT only). *P* value was two-sided.

survival were especially striking for patients with squamous cell carcinoma (Fig. 3) or adenocarcinoma (Fig. 4). For the large-cell histology subtype, there was no difference in survival among 20 patients in the RT group (median survival = 8.9 months) and 24 patients in the CT-RT group (median survival = 9.4 months) (*P* = .714). The observed difference in overall survival remained statistically significant when data analysis was adjusted for sex, age, histologic cell type, and performance status in a Cox model (*P* = .034). The median survival for the entire study population was 11 months. The median survival was 13.7 months for the CT-RT group and 9.6 months for the RT group. Rates of survival in the CT-RT group were 54% after 1 year, 26% after 2 years, 24% after 3 years, 19% after 4 years, 17% after 5 years, and 13% after 6 and 7 years, as compared with 40%, 13%, 10%, 7%, 6%, 6%, and 6%, respectively, for the RT group. Thus, after 5 years, the probability of survival was 2.8 times greater for the patients who received induction chemotherapy in addition to radiation therapy. The survival rate values after 1-3 years of treatment are slightly different compared with those published earlier (*2*) because of small differences in the number of censored observations at the last and the present analyses. Fourteen patients are known to have survived beyond 4 years in the CT-RT group compared with only five in the RT group. The longest period of survival is more than 10 years, which was seen in a patient in the RT group. As previously reported (*11*), the survival advantage conveyed by sequential chemotherapy–radiotherapy was apparent in patients with both stage IIIA and stage IIIB disease on the basis of a retrospective radiographic staging analysis of this same study population.

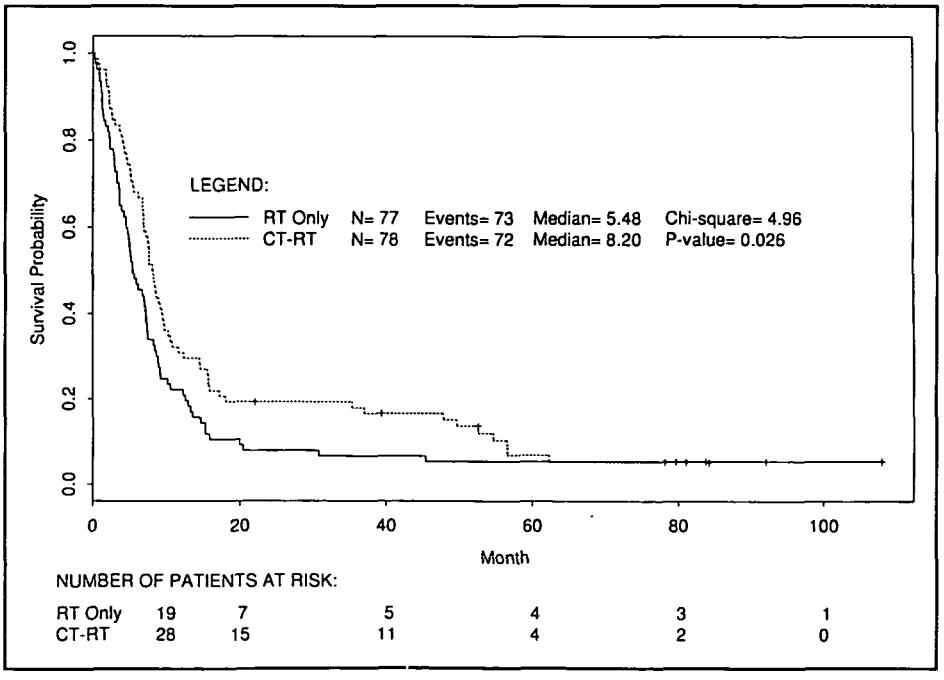

Fig. 2. Treatment failure-free survival of patients with stage III non-small-cell lung cancer after sequential chemotherapy–radiation therapy (CT-RT) compared with that of patients after radiation therapy alone (RT only). *P* value was two-sided.

Objective tumor responses were declared in 44 (56%) of 78 patients in the CT-RT group compared with 33 (43%) of 77 patients in the RT group (*P* = .092). These values are unchanged from those we reported previously (*2*). Within 3 weeks of completing induction chemotherapy, 28 patients (36%) in the CT-RT group already had objective responses; three (4%) had complete responses, 17 (22%) had partial responses, and eight (10%) had regression of evaluable disease. As previously noted, there was no evidence that major deviations from the radiation therapy protocol differed between the arms, and there was no difference in the sites of disease progression, with a high proportion of both local and distant relapses in both groups (*2*). Details regarding the delivery of planned chemotherapy and the toxic effects associated with each treatment arm were previously reported (*2*).

Discussion

This 7-year analysis of CALGB 8433 continues to demonstrate the superiority

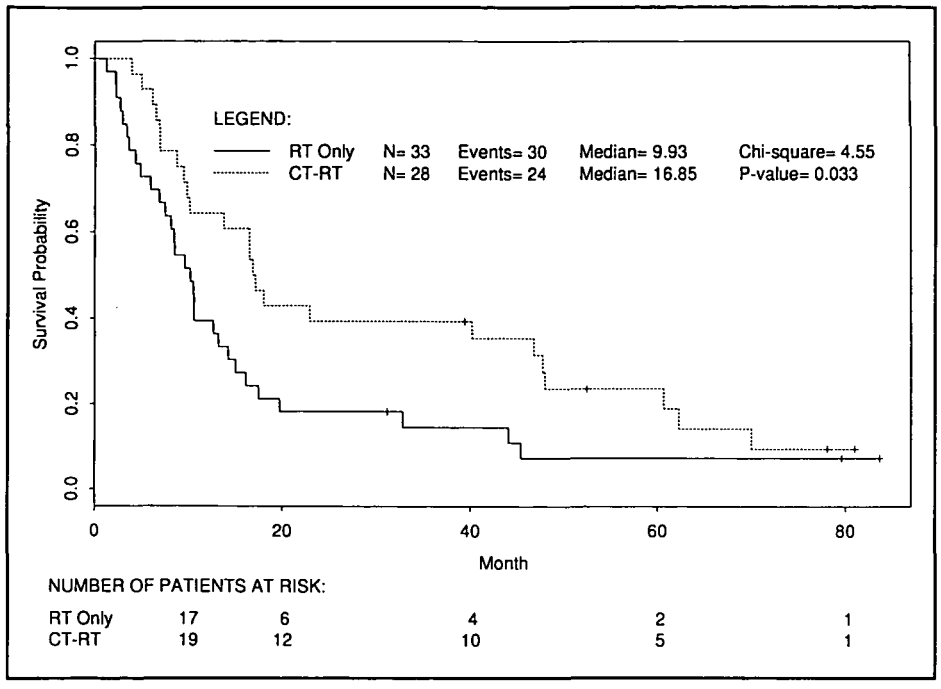

Fig. 3. Survival of patients with stage III non-small-cell lung cancer of squamous cell histology after sequential chemotherapy–radiation therapy (CT-RT) compared with that of patients after radiation therapy alone (RT only). *P* value was two-sided.

of "induction" or "neoadjuvant" chemotherapy followed by radiation therapy over radiation therapy alone in this randomized trial of patients with stage III NSCLC. Early analyses of other randomized trials, which have been reported (*3*,*12*,*13*), also indicate that induction chemotherapy followed by radiation therapy is superior to radiation therapy alone in this subset of lung cancer patients. The intergroup trial conducted by the RTOG and the Eastern Cooperative Oncology Group (ECOG) was specifically designed to confirm the results of the CALGB 8433 trial (*3*). The 1-year and median survival results of that trial are quite similar to those seen in the initial reporting of CALGB 8433 (*1*,*2*) and confirm the early survival benefit of this specific cisplatin–vinblastine induction chemotherapy. A recent international meta-analysis (*14*) also supports the survival advantage of cisplatin-based induction chemotherapy in stage III NSCLC.

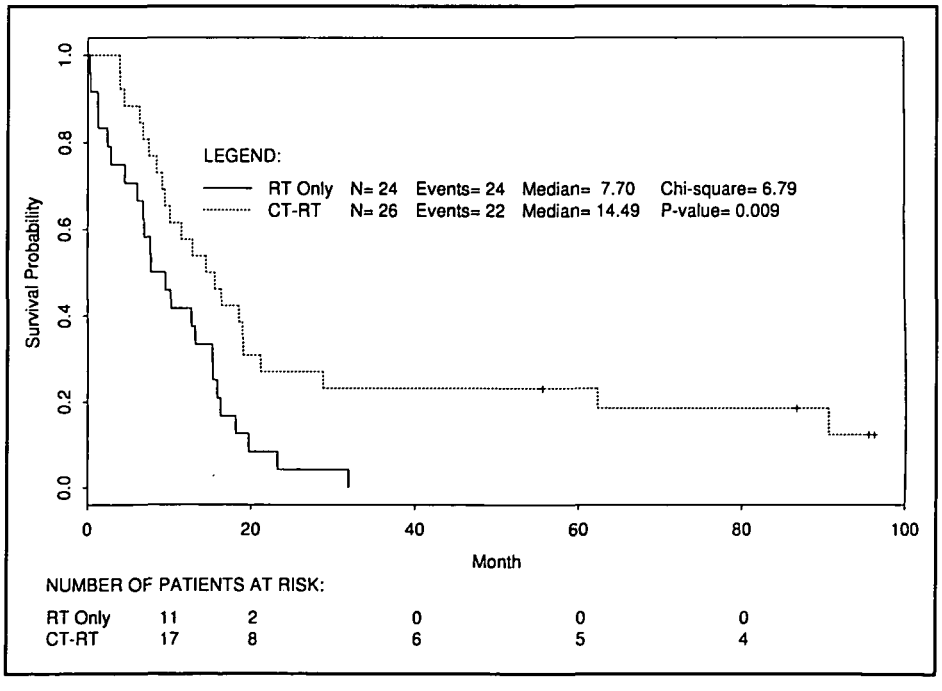

Fig. 4. Survival of patients with stage III non-small-cell lung cancer of adenocarcinoma histology after sequential chemotherapy–radiation therapy (CT-RT) compared with that of patients after radiation therapy alone (RT only). *P* value was two-sided.

When lung cancer was at its zenith of incidence, the American Cancer Society estimated that the number of new patients diagnosed with lung cancer in the United States would be 190 000 in 1994, with a decrease to 170 000 in 1995 (*15*). About 75%-80% of these patients, or about 130 000, would be diagnosed with NSCLC, including the histologies of squamous cell carcinoma, large-cell carcinoma, and adenocarcinoma. About one third of these, or 45 000 patients, would be expected to have stage III disease at the time of diagnosis. Stage III NSCLC is defined by clinical and/or surgical staging at the time of diagnosis. In simple terms, stage III includes absence of demonstrable distant metastases in the setting of invasive disease that is locally extensive, as defined by invasion of other tissues or involvement of mediastinal lymph nodes (*4*,*5*). Stage IIIA disease includes invasion of ipsilateral lymph nodes (N2) close to the carina or invasion into soft-tissue structures that are technically resectable. Such locally extensive disease is highly predictive of the existence of micrometastatic disease and of recurrent regional disease. Even when surgical resection can be performed, few of these patients are cured because of the subsequent appearance of metastatic disease. Stage IIIB disease includes tumors that have invaded vital structures such that surgical resection is not feasible (T4) and/or tumors that have invaded contralateral mediastinal lymph nodes (N3), which usually can be determined only by surgical sampling.

For many years, radiation therapy alone was considered the treatment of choice for patients with stage IIIA or IIIB disease, even though median survival lasted only 9-11 months and 5-year survival rates were only 3%-10% (*16*-*19*). In 1995, stage IIIA or IIIB lung cancer alone was projected to be the seventh most common cancer behind prostate cancer,

breast cancer, other lung cancers, colon cancer, non-Hodgkin's lymphoma, and bladder cancer and to account for about 35 000 deaths per year (making it the fifth most common cause of cancer deaths behind other lung cancers, colon cancer, breast cancer, and prostate cancer). Thus, in stage III NSCLC, treatment changes resulting in even modest improvement in outcome could save a substantial number of lives. If the survival advantages of sequential chemotherapy followed by radiotherapy were to extend to all patients with stage III NSCLC, as many as an additional 5100 patients per year might survive 5 years.

As previously reported (*2*), the survival advantage observed in CALGB 8433 was achieved without a clinically important increase in toxic effects (*2*). The major toxic effects that occurred in a small percentage of patients were severe nausea and/or vomiting, severe anemia, and neutropenic sepsis. In particular, this schedule of sequential chemotherapy–radiation therapy was associated with only a 1% frequency of severe or life-threatening esophagitis or pneumonitis. Despite these results, some physicians continue to question the role of chemotherapy in this setting because they are concerned about its side effects and risk–benefit issues (*20*). For that reason, it is worth noting that, since this trial was conducted, there have been important advances in the supportive care of cancer patients who receive chemotherapy. Specifically, new antiemetic serotonin-antagonist agents such as ondansetron and granisetron substantially decrease the severity of emesis associated with cisplatin chemotherapy (*21*), such that cisplatin is now typically given in the outpatient setting. Erythropoietin can greatly decrease the frequency of severe anemia associated with cisplatin chemotherapy as well as the need for blood transfusions (*22*). Granulocyte and granulocyte–macrophage colony-stimulating factors have been associated with a decrease in the duration of infection-related morbidity related to chemotherapy, even though they do not appear to decrease the frequency of sepsis or to improve outcome from cancer therapy (*23*).

Since completion of CALGB 8433, a number of new agents with activity in NSCLC have become available; they include ifosfamide, paclitaxel (Taxol), and vinorelbine tartrate (Navelbine) (*24,25*). Perhaps one or more of these agents combined with cisplatin would produce results superior to those produced by vinblastine–cisplatin. Related approaches that also appear promising include the use of induction chemotherapy before surgery in patients with operable stage IIIA disease (*26,27*), the use of sequential chemotherapy and radiation therapy before surgery (*28*), and the use of concurrent chemotherapy–radiotherapy before surgery (*29,30*) or as definitive therapy for patients with unresectable tumors (*31*). Many physicians are concerned that some concurrent chemotherapy–radiotherapy approaches are associated with a statistically significant frequency of severe esophagitis and pneumonitis and that increased hematologic toxicity may compromise the delivery of the systemic chemotherapy. The published results of one randomized trial (*31*) have failed to show a survival advantage with concurrent cisplatin–radiotherapy compared with radiotherapy alone (*31*). On the basis of the results of CALGB 8433 and subsequent confirmatory trials, induction cisplatin-based chemotherapy followed by radiation therapy should be considered the standard treatment for stage III NSCLC. However, because 80%-85% of patients still die of this cancer within 5 years, better treatment is still needed. The superiority of new therapies can be established only by rigorous, prospective, randomized trials.

References

(*1*) Dillman RO, Seagren SL, Propert K, Eaton WL, Frey EF, Green MR. Protochemotherapy improves survival in regional non-small cell lung cancer (NSCLC). Proc ASCO 1988;7:195.

(*2*) Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer [*see* comment citations in Medline]. N Engl J Med 1990;323:940-5.

(*3*) Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, 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.

(*4*) Mountain CF. Assessment of the role of surgery for control of lung cancer. Ann Thorac Surg 1977;24:365-73.

(*5*) Mountain CF. A new international staging system for lung cancer. Chest 1986;89(4 Suppl):225S-33S.

(*6*) Green MR, Kramar A, Schilsky R, Stoopler M, Zimmer B, Richards F 2d, et al. Platinum-based combination chemotherapy in advanced non-small cell lung cancer: a randomized phase II trial of the Cancer and Leukemia Group B. Med Pediatr Oncol 1990;18:197-202.

(*7*) Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer 1987;59:1874-81.

(*8*) Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Soc 1958;53:457-81.

(*9*) Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35:1-39.

(*10*) Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.

(*11*) Kreisman H, Lisbona A, Olson L, Propert KJ, Modeas C, Dillman RO, et al. Effect of radiologic stage III substage on nonsurgical therapy of non-small cell lung cancer. Cancer 1993;72:1588-96.

(*12*) Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients [*see* comment citation in Medline]. J Natl Cancer Inst 1991;83:417-23.

(*13*) Schaake-Koning C, Maat B, van Houtte P, van den Bogaert W, Dalesio O, Kirkpatrick A, et al. Radiotherapy combined with low-dose cis-diammine dichloroplatinum (II) (CDDP) in inoperable nonmetastatic non-small cell lung cancer (NSCLC): a randomized three arm phase II study of the EORTC Lung Cancer and Radiotherapy Cooperative Groups. Int J Radiat Oncol Biol Phys 1990;19:967-72.

(*14*) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised trials. Non-small Cell Lung Cancer Collaborative Group [*see* comment citation in Medline]. BMJ 1995;311:899-909.

(*15*) Wingo PA, Tong T, Bolden S. Cancer statistics, 1995 [published erratum appears in CA Cancer J Clin 1995;45:127-8]. CA Cancer J Clin 1995;45:8-30.

(*16*) Roswit B, Patno ME, Rapp R, Veinbergs A, Feder B, Stuhlbarg J, et al. The survival of patients with inoperable lung cancer: a large-scale randomized study of radiation therapy versus placebo. Radiology 1968;90:688-97.

(*17*) Johnson DH, Einhorn LH, Bartolucci A, Birch R, Omura G, Perez CA, et al. Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer [*see* comment citations in Medline]. Ann Intern Med 1990;113:33-8.

(*18*) Dillman RO, Berry C, Ryan KP, Green MR, Seagren SL. Recent outcomes for patients with carcinoma of the lung. Cancer Invest 1991:9:9-17.

(*19*) Payne DG. Non-small-cell lung cancer: should unresectable stage III patients routinely

receive high-dose radiation therapy? J Clin Oncol 1988;6:552-8.
(20) Raby B, Pater J, Mackillop WJ. Does knowledge guide practice? Another look at the management of non-small-cell lung cancer. J Clin Oncol 1995;13:1904-11.
(21) Hesketh PJ, Gandara DR. Serotonin antagonists: a new class of antiemetic agents. J Natl Cancer Inst 1991;83:613-20.
(22) Henry DH, Brooks BJ Jr, Case DC Jr, Fishkin E, Jacobson R, Keller AM, et al. Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. Cancer J Sci Am 1995;1:252-60.
(23) Demetri GD, Griffin JD. Granulocyte colony-stimulating factor and its receptor. Blood 1991;78:2791-808.
(24) Lilenbaum RC, Green MR. Novel chemotherapeutic agents in the treatment of non-small-cell lung cancer. J Clin Oncol 1993;11:1391-402.
(25) Ihde DC. Chemotherapy of lung cancer. N Engl J Med 1992;327:1434-41.
(26) Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee LS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer [*see* comment citation in Medline]. J Natl Cancer Inst 1994;86:673-80.
(27) Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canto A, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer [*see* comment citations in Medline]. N Engl J Med 1994;330:153-8.
(28) Strauss GM, Herndon JE, Sherman DD, Mathisen DJ, Carey RW, Choi NC, et al. Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small-cell carcinoma of the lung: report of a Cancer and Leukemia Group B phase II study. J Clin Oncol 1992;10:1237-44.
(29) Weiden PL, Piantadosi S. Preoperative chemotherapy (cisplatin and fluorouracil) and radiation therapy in stage III non-small-cell lung cancer: a phase II study of the Lung Cancer Study Group. J Natl Cancer Inst 1991;83:266-73.
(30) Albain K, Rusch V, Crowley J, Turrisi A, Rice T, Livingston R. Concurrent cisplatin/etoposide (PE) + chest radiation (CRT) followed by surgery for stages 3A(N2) and 3B non-small cell lung cancer: completed analysis of SWOG-8805. Proc ASCO 1994;13:337.
(31) Blanke C, Ansari R, Mantravadi R, Gonin R, Tokars R, Fisher W, et al. Phase III trial of thoracic irradiation with or without cisplatin for locally advanced unresectable non-small-cell lung cancer; a Hoosier Oncology Group protocol. J Clin Oncol 1995;13:1425-9.

Notes

R. O. Dillman and M. R. Green have participated in company-sponsored speaker bureaus and/or have investment funds that include small quantities of common stocks for various pharmaceutical and biotechnology companies whose products are mentioned in this report.

Presented in part at the 29th annual meeting of the American Society of Clinical Oncology, Orlando, FL, May 1993.

Manuscript received February 21, 1995; revised April 29, 1996; accepted June 4, 1996.