VOLUME 23 · NUMBER 25 · SEPTEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of Sequential Chemoradiotherapy Compared With Concurrent Chemoradiotherapy in Locally Advanced Non–Small-Cell Lung Cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Français de Pneumo-Cancérologie NPC 95-01 Study

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Submitted March 9, 2004; accepted October 26, 2004.

Supported by a grant from Pierre Fabre Institute of Oncology, Boulogne, France.

Presented in part at the 37th Annual Meeting of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001.

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

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0732-183X/05/2325-5910/$20.00

DOI: 10.1200/JCO.2005.03.070

ABSTRACT

Purpose

We conducted a phase III study to compare the survival impact of concurrent versus sequential treatment with radiotherapy (RT) and chemotherapy (CT) in unresectable stage III non–small-cell lung cancer (NSCLC).

Patients and Methods

Patients were randomly assigned to one of the two treatment arms. In the sequential arm, patients received induction CT with cisplatin (120 mg/m^2) on days 1, 29, and 57, and vinorelbine (30 mg/m^2/wk) from day 1 to day 78, followed by thoracic RT at a dose of 66 Gy in 33 fractions (2 Gy per fraction and 5 fractions per week). In the concurrent arm, the same RT was started on day 1 with two concurrent cycles of cisplatin 20 mg/m^2/d and etoposide 50 mg/m^2/d (days 1 to 5 and days 29 to 33); patients then received consolidation therapy with cisplatin 80 mg/m^2 on days 78 and 106 and vinorelbine 30 mg/m^2/wk from days 78 to 127.

Results

Two hundred five patients were randomly assigned. Pretreatment characteristics were well balanced between the two arms. There were six toxic deaths in the sequential arm and 10 in the concurrent arm. Median survival was 14.5 months in the sequential arm and 16.3 months in the concurrent arm (log-rank test $P = .24$). Two-, 3-, and 4-year survival rates were better in the concurrent arm (39%, 25%, and 21%, respectively) than in the sequential arm (26%, 19%, and 14%, respectively). Esophageal toxicity was significantly more frequent in the concurrent arm than in the sequential arm (32% *v* 3%).

Conclusion

Although not statistically significant, clinically important differences in the median, 2-, 3-, and 4-year survival rates were observed, with a trend in favor of concurrent chemoradiation therapy, suggesting that is the optimal strategy for patients with locally advanced NSCLC.

J Clin Oncol 23:5910-5917. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Approximately 30% of patients with non–small-cell lung cancer (NSCLC) have unresectable locally advanced disease at diagnosis (mainly stage IIIB). In the late 1980s, radiotherapy was the standard treatment for these patients. Randomized trials[1,2] and a 1995 overview[3] subsequently showed that combination chemoradiotherapy was superior to

radiotherapy alone. Clinical practice guidelines now recommend such combination therapy.[4,5] At the design stage of our trial, the standard treatment of unresectable non–small-cell lung cancer was chemotherapy followed by radiation.[6-8]

Numerous clinical trials were conducted in the 1990s to determine the best combination of chemotherapy and radiotherapy and to examine whether concomitant chemoradiotherapy was appropriate in this setting.[9] The use of chemotherapy (especially carboplatin) to induce radiosensitization showed no survival benefit in phase III trials.[10,11] However, several studies showed the feasibility of the cisplatin-etoposide combination plus radiotherapy for patients with stage III disease.[12-15]

Other trials have compared concurrent versus sequential chemoradiotherapy, but they used "old" regimen platinum derivates, combined with vinblastine or vindesine and mitomycin C.[16,17] Two randomized phase III trials are available.[16,17] A Japanese trial[16] and a more recent North American study[17] both showed a survival benefit with the concurrent strategy (17 *v* 14.6 months). More recent phase II trials have tested new drugs.[18,19] Zatloukal et al[20] presented the results of a randomized phase II trial also favoring concomitant therapy.

The French Pneumology Group (GFPC) had previously conducted a comparative trial of two different chemotherapy regimens in stage III disease, showing that vinorelbine was the best drug to be combined with platinum.[21] Two French groups (Groupe Lyon-Saint-Etienne d'Oncologie Thoracique [GLOT] and GFPC) then jointly conducted a trial (the GLOT-GFPC NPC 95-01 study) designed to test this regimen in combination with radiation therapy, given either sequentially or concurrently. However, as vinorelbine was not authorized in France for combination with radiotherapy in 1995, etoposide was used in the concurrent treatment arm, while cisplatin-vinorelbine was used sequentially. The primary end point was survival rate.

PATIENTS AND METHODS

Eligibility Criteria

This multicentric randomized phase III study was started in October 1996. Eligible patients were aged between 18 and 70 years, had an Eastern Cooperative Oncology Group score ≤ 1, and had $\leq 10\%$ weight loss in the 3 months before inclusion. They were required to have previously untreated histologically or cytologically proven NSCLC, unresectable stage IIIA-N2 disease, or a stage IIIB disease without pleural involvement. Inoperability and N2 extension were defined on the basis of computed tomography (CT) scan after local panel discussion among surgeons, chest physicians, oncologists, and radiotherapists. Mediastinoscopy was not mandatory. Stage IIIB disease was assigned either by N3 (controlateral mediastinal or supraclavicular nodes) or by T4 from invasion of mediastinal structures. The following laboratory values were required: neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, AST and ALT $\leq 2\times$ the upper limit of the institutional normal range, total bilirubin $\leq 1.25\times$ the upper limit of the institutional normal range, and creatinine concentration ≤ 120 μmol/L. No hemoglobin cutoff was set.

Patients were also required to have at least one unidimensionally measurable target lesion ≥ 2 cm by CT scan. Ineligibility criteria were as follows: active uncontrolled infection, or fever greater than 38.3°C; unstable cardiovascular disease; and previous malignancy (except for in situ carcinoma of the cervix or adequately treated cutaneous basal or squamous cell carcinoma). Adequate pulmonary function was required, with forced expiratory volume in 1 second $\geq 40\%$ of normal and partial arterial oxygen pressure ≥ 60 mmHg. All patients were required to provide written informed consent, and the protocol was approved by the institutional ethics committee.

Pretreatment and Follow-Up Evaluations

Before enrollment, the patients gave their full medical histories and underwent physical examination with assessment of performance status (PS). Laboratory investigations included complete and differential blood counts and assays of electrolytes, glucose, calcium, albumin, transaminases, alkaline phosphatases, total bilirubin, and creatinine. An ECG was recorded. The following examinations had to be performed within the month preceding entry to the study: chest x-ray, bronchoscopy, chest and brain CT scan, abdominal CT scan or sonography, radionuclide bone scan, and spirometry.

CBCs were done every week throughout the study. Every 28 days, patients underwent a clinical examination focusing on cancer-related symptoms and treatment toxicities. On these occasions, all the above laboratory tests were repeated, together with chest x-ray and ECG. Toxicity was graded according to standard WHO criteria. In the sequential arm, responses were assessed after the three cycles of chemotherapy and 4 weeks after the end of radiation therapy; and in the concurrent arm, 4 weeks after the end of radiation-chemotherapy and 8 weeks after the end of the consolidation chemotherapy. In both arms, the final evaluation was done 162 days after treatment initiation. Imaging studies could be repeated at all times if clinically indicated (to confirm clinical or radiological progression, for example). Complete and partial responses were based on WHO criteria.[22] A panel reviewed the imaging studies for staging and response evaluation. Follow-up visits were conducted every 3 months.

Treatment Schedule

Patients were stratified by stage (IIIA-N2/IIIB) and were then randomly assigned to receive sequential or concurrent therapy.

In the sequential arm, three cycles of chemotherapy were administered first, consisting of cisplatin 120 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1, 8, 15, and 21, repeated every 4 weeks. Doses were adjusted if necessary according to blood cell counts and renal function: vinorelbine was administered at full dose unless the neutrophils count was $\leq 1.5 \times 10^9$/L or the platelet count was $\leq 100 \times 10^9$/L. Half-dose vinorelbine and full-dose cisplatin were administered if the neutrophils count was between 1.0 and 1.5×10^9/L or if the platelet count was between 75 and 100×10^9/L. If the neutrophil count was $\leq 1.0 \times 10^9$/L or if the platelet count was $\leq 75 \times 10^9$/L, the single vinorelbine administration was omitted, and administration of the two drugs was delayed until recovery, with a maximum delay of 7 days. Patients with progressive disease after chemotherapy were considered to have treatment failure and were withdrawn from the study. For patients with an objective response or no change after chemotherapy, the radiotherapy began 4 weeks after the third cisplatin

administration. Radiotherapy consisted of 66 Gy in 33 fractions of 2 Gy each, for 5 days a week given over a period of 6.5 weeks. The target volume included the initial primary tumor, the homolateral hilar and mediastinal areas, and a 1.5- to 2.0-cm margin. The controlateral hilar area and supraclavicular fossa were not systematically included. The homolateral supraclavicular fossa was systematically treated in patients with upper-lobe tumors. The paraesophageal and inferior pulmonary ligament nodal regions were included if the lesion was in the lower lobe. Radiotherapy was delivered with photon beams generated by a linear accelerator, with an energy exceeding 6 MV. In sequential arm, it was recommended to consider initial tumor volume before induction chemotherapy. The radiation field could be reduced after a dose of 40 Gy had been reached. For the spinal cord, the maximum dose was 46 Gy to any point. Beyond this dose, the spinal cord was excluded from the irradiated volume by using parallel-opposed oblique fields. All fields had to be treated every day. A short break of less than 1 week was allowed if grade 3 or 4 esophagitis, weight loss $\geq$ 10% from baseline, grade 4 febrile neutropenia, or grade 4 thrombocytopenia occurred. If radiotherapy had to be delayed for more than 7 days, the patient was withdrawn from the study.

Chemotherapy and radiotherapy began simultaneously in the concurrent arm. The radiotherapy schedule was identical to that in the sequential arm. The first cycle with cisplatin 20 mg/m^2 and etoposide 50 mg/m^2 was administered on days 1 to 5, and the second 5-day cycle was administered 4 weeks later, beginning on day 29. If radiotherapy had to be interrupted because of toxicity, the patient was withdrawn from the study, but was included in the survival analysis. On day 78, 4.5 weeks after the end of the 6.5 weeks of radiotherapy, two cycles of consolidation chemotherapy began, consisting of cisplatin 80 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1, 8, 15, and 21, repeated every 4 weeks. The same rules as for induction chemotherapy in arm A were used for dose adjustments and delays, depending on hematologic toxicity.

In both arms, symptomatic treatment was started as soon as esophagitis occurred (grade 1). It systematically combined a proton pump inhibitor, anti-infective therapy in case of clinical mycosis, and steroids and analgesics for grade 2 esophagitis.

Study Design and Statistical Analysis

This was a prospective, unblinded, randomized study. The central office stratified patients according to institute and stage (IIIAN2/IIIB). The primary end point was the survival rate. To detect an improvement in 2-year survival, from 20% in sequential arm to 35% in concurrent arm, with an α risk of .05 and a β risk of .15 in a one-sided test, the required sample size was 210 patients. One hundred sixty deaths were expected.

Survival was calculated from date of random assignment to death or last follow-up evaluation. Survival curves were established with the Kaplan-Meier method and were compared using the log-rank test and the Cox model. Usual statistical tests (χ^2 test, Fisher's exact probability test, and the Mann-Whitney U test) were used to compare variables between the two populations. The influence of variables on survival was studied by univariate and multivariate analyses (Cox model). Multivariate analysis of variables predictive of survival was based on a logistic regression model. All tests were run on Statview version 5.0 statistical software (SAS Institute Inc, Cary, NC). Differences were considered significant at $P < .05$.

RESULTS

Patients

From October 1996 to May 2000, 212 patients were enrolled in 30 participating institutions. Six centers enrolled a total of 112 patients, while 12 centers each enrolled fewer than five patients. Seven patients were not eligible after panel file revue (three in the sequential arm and four in the concurrent arm); six patients had stage IV disease, and one had pleural effusion. All these patients were initially considered to have stage IIIB disease. Thus, 205 patients (103 in the sequential arm and 102 in the concurrent arm) were assessable for survival, and 193, for toxicity. Four patients were lost to follow-up.

The characteristics of 201 patients are listed in Table 1. Two patients initially considered to have stage IIIAN2 disease were reclassified as T3N1M0 after file revue. The number of patients with stage IIIB disease was higher in the sequential arm, though the difference was not significant. This imbalance emerged after panel file review following random assignment. Eight patients were reclassified: six in the sequential arm and two in the concurrent arm. All prognostic factors were well balanced between the two treatment arms. There was no difference in the baseline hemoglobin level (median, 13 g/dL).

Table 1. Patient Characteristics

Characteristic	Sequential Treatment	Concurrent Treatment	*P*
No. of eligible patients	101	100	
Age, years			
Median	56	57	.55
Range	38-70	38-69	
Sex			
Male	91	85	.19
Female	10	15	
Performance status			
0	56	51	.62
1	45	49	
Weight loss $\geq$ 10%	5	5	
Histology			
Squamous cell	56	60	.51
Adenocarcinoma	30	23	
Large cell	15	17	
Stage of disease			
IIIAN2	18	33	.08
IIIB	81	67	
TNM			
T3N1M0	2	0	.06
T1-3N2M0	18	33	
T1-3N3M0	31	20	
T4N0-1M0	9	6	
T4N2-3M0	41	41	
N3 disease	40	34	.13
Supraclavicular lymph node	12	11	

Treatment Delivery and Toxicities

Sixty patients (59.4%) in the sequential arm and 88 patients (88%) in the concurrent arm received ≥ 60 Gy of radiotherapy ($P < .001$). Twenty-three (23%) patients in the sequential arm received fewer than three cycles of induction chemotherapy for the following reasons: acute severe toxicity in 17 patients, disease progression during chemotherapy in five patients, and refusal to continue chemotherapy after the first course in one case. In the concurrent arm, 54 patients (54%) received the two planned cycles of consolidation chemotherapy, and seven patients (7%) received only one course. Thirty-nine patients (39%) received no consolidation chemotherapy for the following reasons: disease progression on restaging after concurrent therapy in 16 patients, residual toxicity of chemoradiation in 14 patients, patient refusal in three, myocardial infarction in one, and unknown reasons in five patients.

Treatment had to be stopped for acute severe toxicity in 19 patients (18%) in the sequential arm and 23 patients (23%) in the concurrent arm. This toxicity was due to chemotherapy alone in 17 and 11 patients, respectively. Two permanent treatment cessations occurred during radiotherapy in the sequential arm, and 12 occurred during chemoradiation in the concurrent arm (for acute esophagitis in five cases).

Treatment-related toxicities are listed in Table 2. The incidence of neutropenia, including grade 4 neutropenia, was higher with the sequential treatment than with the concurrent treatment ($P = .008$). Peripheral neuropathies were also more frequent in the sequential arm. Acute esophagitis was more frequent with concurrent therapy ($P < .0001$). Radiation pneumonitis tended to be less frequent in the concurrent arm. Six toxic deaths were observed in the sequential arm (5.6%), and 10 (9.5%) in the concurrent arm. In each treatment arm, three deaths were related to chemotherapy alone (two cases of fatal febrile aplasia during consolidation chemotherapy in concurrent arm). Seven patients died from toxicity related to concurrent chemoradiation therapy, four of massive pulmonary hemorrhage. In the sequential arm, three deaths were considered related to radiotherapy (one from pulmonary hemorrhage). The 10 toxic deaths in the concurrent arm occurred within 6 months after inclusion, compared to three early toxic deaths in the sequential arm. The causes of early death occurring are listed in Table 3.

Table 2. Toxicity (WHO grade) by Treatment Arm

Toxicity	Sequential Treatment (n = 100)		Concurrent Treatment (n = 93)		*P*
Grade 3-4 neutropenia	88	88	72	77	.05
Grade 4 neutropenia	72	72	45	48	.008
Grade 3-4 anemia	28	28	19	20	.22
Grade 3-4 thrombocytopenia	15	15	15	16	.82
Grade 3-4 infection	12	12	13	14	.68
Renal failure grade 1-2	15	15	8	8.5	.17
Peripheral neuropathy:					
Grade 1	18	18	11	12	.23
Grade 2	7	7	3	3	.23
Grade 3	4	4	0	0	.05
Esophagitis grade 3-4	3	3	30	32	< .0001
Mucositis grade > 2	3	3	3	5	.40
Nausea-vomiting grade 3-4	18	18	22	24	.33
Pneumonitis grade 3-4	11	11	5	5	.17

Response

The objective response rate was evaluated at the end of each treatment sequence. Seventy-eight patients (78%) were assessable for the response in the sequential arm, and 68 (68%), in the concurrent arm. Three complete responses and 39 partial responses were obtained with the sequential treatment (50%). Six complete responses and 27 partial responses were obtained in the concurrent arm (40%). The response rates were 54% with sequential treatment and 49% with concurrent treatment (all assessable patients), and, respectively, 41% and 32% (intent to treat analysis). The differences were not statistically significant ($P = .56$). The disease stabilized in five patients in the sequential arm and in eight patients in the concurrent arm. At the end of treatment, 15 patients in the sequential arm and 12 patients in the concurrent arm had progressed. Early progression (during therapy) occurred in 16 patients in each treatment arm.

Survival

Survival was analyzed on April 1, 2003, after a median follow-up of 4.8 years. The median survival was 14.5 months (95% CI, 8.3 to 27.4) in the sequential arm and 16.3 months (95% CI, 5.8 to 34.8) in the concurrent treatment. The 1-, 2-, 3-, and 4-year survival rates were 59.8% (95% CI, 50% to 69%), 26.5% (95% CI, 17.9% to 35%), 18.6% (95% CI, 11% to 26%), and 14.2% (95% CI, 7% to 21.2%), respectively, in the sequential arm, and 60.4% (95% CI, 50.8% to 69.9%), 39.3% (95% CI, 29.7% to 48.9%), 24.8% (95% CI, 16.2% to 33.3%), and 20.7% (95% CI, 12.3% to 29%), respectively, in the concomitant arm (log-rank test, $P = .24$; Fig 1). The 1-, 2-, 3-, and 4-year progression-free

Table 3. Early Deaths Less Than 6 Months After Treatment Outset

Cause of Death	Sequential Treatment (n = 17)	Concurrent Treatment (n = 25)
Treatment-related deaths	3	10
Febrile neutropenia	3	3
Massive hemoptysis	0	4
Radiation pneumonitis	0	2
Esophagitis + infection	0	1
Progressive disease	13	13
Other	1	2

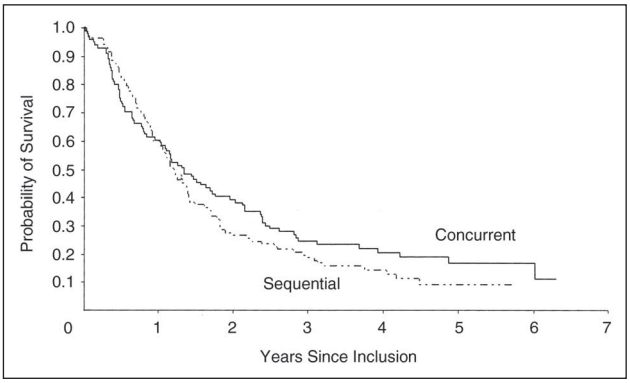

Fig 1. Overall survival according to the treatment in the Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Français de Pneumo-Cancérologie NPC 95-01 study.

survival rates were 39.2% (95% CI, 29.7% to 48.7%), 16.6% (95% CI, 9% to 23.9%), 9.8% (95% CI, 4% to 15%), and 8.8% (95% CI, 3% to 14%), respectively, in the sequential arm, and 42.5% (95% CI, 32.9% to 52.2%), 29.5% (95% CI, 20.5% to 38.4%), 19% (95% CI, 11.3% to 26.8%), and 15% (95% CI, 7% to 22%), respectively, in the concurrent arm (log-rank test, $P = .33$; Fig 2).

Five patients were able to undergo surgery (one in the sequential arm after induction chemotherapy), but all died from local recurrence within 34 months. In the concurrent arm, three patients were able to undergo surgery after completing the full treatment course; one patient is still alive at 5 years, while the other two died from distant metastasis at 24 and 32 months. One patient underwent surgery after the concurrent therapy and died of pulmonary embolism at 19 months without relapsing.

In multivariate analysis, only PS (0 *v* 1; $P = .02$) and sex (female *v* male; $P = .04$) were significantly related to survival. Disease stage (IIIAN2/IIIB; $P = .051$), treatment arm (concurrent *v* sequential; $P = .09$), and the baseline hemoglobin level ($\leq$ 12 g/dL *v* $>$ 12 g/dL; $P = .32$) were not significantly related to survival.

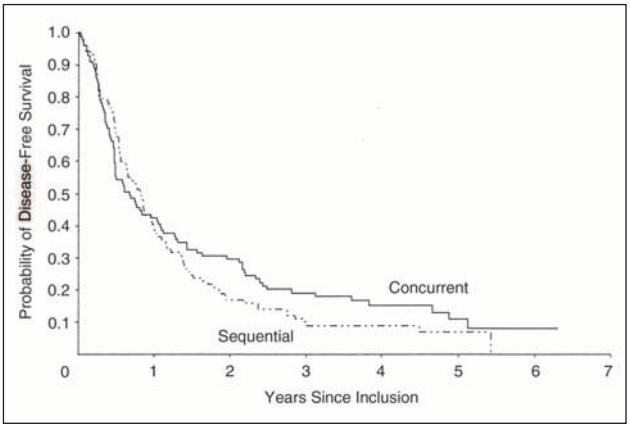

Fig 2. Disease-free survival according to the treatment in the Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Français de Pneumo-Cancérologie NPC 95-01 study.

Patterns of Failure

Sites of initial relapse are listed in Table 4. Isolated locoregional relapses (primary tumor and/or regional nodes) were more frequent in the sequential arm than in the concurrent arm, whereas the number of distant relapses was similar in the two arms. The difference between the two arms was not statistically significant ($P = .17$). There were 10 cases of isolated brain progression in the sequential arm, and six, in the concurrent arm.

DISCUSSION

Only one randomized phase III trial comparing sequential and concurrent administration of chemotherapy and radiation therapy for NSCLC has been published so far.[16] In the study by Furuse et al,[16] chemotherapy combined cisplatin, vindesine, and mitomycin C. The total dose of radiotherapy was 56 Gy, and, in the concurrent arm, was administered in a split-course schedule, with a rest period of 10 days. Median survival was significantly better with concurrent therapy than with sequential therapy (16.5 and 13.3 months, respectively; $P = .0398$). The 2-, 3-, and 5-year survival rates were, respectively, 34.6%, 22.3%, and 15.8% in the concurrent arm, and 27.4%, 14.7%, and 8.9% in the sequential arm. Radiation Therapy Oncology Group (RTOG) study 94-10[17] compared sequential treatment, corresponding to the best arm of the study of Dillman et al[6] with concurrent therapy, in which the same dose of radiotherapy (63 Gy) was administered during the two cycles of cisplatin-vinblastine therapy, and with concurrent treatment using a bi-fractionated and accelerated irradiation (69.6 Gy) combined with two cycles of cisplatin-etoposide. The median survival rate in the concurrent treatment with cisplatin-vinblastine and standard radiotherapy was significantly better than that in the sequential arm (17 *v* 14.6 months; $P = .046$), and fell between these values (15.2 months) in the concurrent therapy arm with bi-fractionated irradiation ($P = .296$). The survival rates at 4 years were, respectively, 12%, 21%, and 17%.

Table 4. Patterns of Failure

Sites of Failure*	Sequential Treatment (n = 75)	Concurrent Treatment (n = 58)
Locoregional only	40	24
Distant only	23	27
Locoregional + distant	12	7

*$P = .17$.

Our study compared sequential and concurrent chemoradiation therapy in locally advanced NSCLC. We found a benefit of concurrent therapy in terms of overall and progression-free survival, though the difference was not significant with the log-rank test ($P = .24$). Furthermore, the 4-year overall and progression-free survival rates were higher in the concurrent arm (20.7% and 15%) than in the sequential arm (14.2% and 8.8%, respectively). The benefit is maintained in the long-term. The difference in overall survival between the two strategies, 6.2% at 3 years and of 6.5% at 4 years, is apparently constant. Our 2-, 3-, and 4-year survival rates are similar to those found in the Japanese study[16] and in the RTOG 94-10 study.[17] The median survival time of 16.3 months in our concurrent treatment arm is also similar to that found in the Japanese study (16.5 months)[16] and in the best concurrent treatment arm of the RTOG study (17 months).[17] The lack of a significant survival difference between sequential and concurrent therapy in our study might be related to a lack of statistical power, or alternatively, to the excess of early deaths in the concurrent arm (25 *v* 17, respectively), particularly toxic deaths (10 *v* 3, respectively).

Multivariate analysis emphasized the role of the classical factors PS and sex in the survival of our patients. While disease stage was not balanced between the two arms, we did not find that stage was associated with survival.

Our chemotherapy schedule was subject to the French vinorelbine licensing terms at the time of the study. The induction chemotherapy with three cycles of cisplatin-vinorelbine in the sequential arm is similar to the schedule used by Le Chevalier et al in a multicenter study.[23] When our study was designed, no data were available on concurrent radiotherapy and chemotherapy with cisplatin-vinorelbine, whereas the cisplatin-etoposide combination was mostly used concurrently with radiotherapy.[12-15] Consolidation chemotherapy with two cycles of cisplatin-vinorelbine was administered in the concurrent arm in order to balance the dose of cisplatin in the two treatment arms. This consolidation chemotherapy administered after concurrent chemoradiation seems promising in terms of survival, as shown in the Southwest Oncology Group (SWOG) S9504 and Locally Advanced Multimodality Protocol (LAMP) studies.[27,28] In our study, 39 patients (39%) did not receive the planned consolidation chemotherapy, mainly because of disease progression after chemoradiation and residual adverse effects of chemoradiation. In the study of Furuse et al,[16] 79 (59%) of the 156 patients in the concurrent arm received one or two cycles of consolidation chemotherapy after chemoradiation. In the SWOG S9504 study,[27] 49 (59%) of the 83 relevant patients received all three cycles of docetaxel consolidation. These data illustrate the difficulties of administering consolidation chemotherapy after concurrent chemoradiation.

In our study, the local relapse rate was lower in the concurrent arm than in the sequential arm, but the difference was not significant. In the RTOG 94-10 study,[17] local failure rates at 2 years were significantly lower with bi-fractionated radiotherapy (25%) than with the sequential therapy (38%) and with other concurrent treatment (33%). Thus, it seems that the superior survival observed with concurrent treatment is associated with better local control. We observed a low objective response rate in both arms, but it should be noted that all patients who did not receive the full treatment were considered nonassessable for the response at the end of therapy. All cases were reviewed by a panel to determine exact response rates. Complete responses had to be confirmed by negative bronchoscopy and biopsy 1 month after the end of treatment. Early progression rates were identical in the two arms. Brain metastasis was frequently the first site of failure and represents a real problem, as in other studies.[15,27]

Major toxicity was observed in our study, and the number of toxic deaths was too high. Among the 16 toxic deaths observed, seven were related to concurrent chemoradiation therapy. This number might be overestimated, however, as all cases of fatal pulmonary hemorrhage in both arms, whether they occurred during or after irradiation, were considered treatment related. Six deaths were due to febrile aplasia; the three cases in the sequential arm might have been due to the high doses of cisplatin-vinorelbine based on the Le Chevalier et al study.[23] Two of the three cases in the concurrent arm occurred during consolidation with cisplatin-vinorelbine. All the toxic deaths involved patients with stage IIIB disease, but neither PS nor the volume irradiated was predictive of vital outcome. We also observed four cases of grade 3 neuropathy in the sequential arm, probably owing to the high cisplatin doses used. The incidence of grade 3 to 4 esophagitis was higher than in the Japanese study, but was similar to that observed in the RTOG 94-10 study and in other phase II studies. We used a standard radiotherapy schedule delivering a total dose of 66 Gy. The split-course administration in the Japanese study might explain the lower incidence of esophagitis. However, the number of permanent treatment interruptions for toxicity was higher with concurrent treatment.

In conclusion, although not statistically significant, clinically important differences in the median, 2-, 3-, and 4-year survival rates were observed, and these results favor concurrent chemoradiation therapy for patients with unresectable stage III NSCLC. Given the high toxicity of this schedule, it should be reserved for patients younger than 70 years, having good PS (0 or 1) and minimal weight loss. The esophagitis represents the dose-limiting toxicity of this combination and could be reduced by using a conformal thoracic radiation as shown by Socinski et al.[24] Conformal thoracic radiation allows dose escalating and can probably improve survival and local control. At this time, the use of amifostine does not seem to significantly reduce the esophageal toxicity of the concomitant chemoradiotherapy.[25,26] New drugs, such as taxanes, vinorelbine, and gemcitabine,

are currently being tested in combination with radiation.[19] Further studies are required to determine the optimal drug combinations and therapeutic strategy.[27,28]

Appendix

Additionnal participating institutions and specialists: Sainte-Marguerite University Hospital, Marseille (J.P. Kleisbauer); General Hospital, Meaux (F. Blanchon, M. Grivaux); Conception University Hospital, Marseille (C. Boutin, P. Astoul); North University Hospital Marseille (D. Charpin, P. Astoul); University Hospital, Toulouse (P. Carles, M.C. Pujazon); General Hospital, Antibes (J.M. Chavaillon); General Hospital, Draguignan (H. Le Caer); University Hospital, Bois-Guillaume (D. Paillotin); University Hospital, Rouen (L. Thiberville); General Hospital, Aix en Provence (R. Poirier, F. Mouysset); General Hospital, Valence (R. Riou); University Hospital, Bordeaux (A. Taytard, J.M. Vernejoux, R. Trouette); Sainte-Eugénie University Hospital, Lyon (Y. Pacheco, S. Dussopt-Guibal, L. Vincent); General Hospital, Macon (D. Arpin); General Hospital, Vienne (C. Marichy); General Hospital, Roanne (C. Bonnamour, J.P. Suchaud); Louis Pradel University Hospital, Lyon (J.F. Cordier, L. Falchero); Centre Leon Bérard, Lyon (I. Martel-Lafay); General Hospital, Saint-Brieuc (D. Coetmeur); Hospitalor, Forbach (V. Mayer); General Hospital, Mulhouse (P. Bombaron); Saint-Anne Army Hospital, Toulon (H. Berard).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or 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.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Alain Vergnenégre					Eli Lilly (A); SanofiAventis (A)			

Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

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