Oral Vinorelbine and Cisplatin with Concurrent Radiotherapy After Induction Chemotherapy with Cisplatin and Docetaxel for Patients with Locally Advanced Non-small Cell Lung Cancer

The GFPC 05-03 Study

Renaud Descourt, MD, Alain Vergnenegre, MD, PhD,† Fabrice Barlesi, MD, PhD,‡ Herve Lena, MD,§ Pierre Fournel, MD,‖ Lionel Falchero, MD,¶ Henri Berard, MD,# Jose Hureaux, MD, PhD,** Herve Le Caer, MD,†† Jean Michel Chavaillon, MD,‡‡ Laurence Geriniere, MD,§§ Isabelle Monnet, MD,‖‖ Stéphane Chouabe, MD,¶¶ Gilles Robinet, MD,* and the GFPC VINCR Team*

Introduction: The aim of this multicenter phase II trial was to evaluate the combination of oral vinorelbine and cisplatin with radiotherapy (RT) after cisplatin-docetaxel induction chemotherapy (CT) in patients with locally advanced non-small cell lung cancer (NSCLC).

Patients and Methods: Patients with previously untreated, inoperable, histologically or cytologically confirmed stage IIIA or IIIB NSCLC, with performance status ≤1 and weight loss ≤10% received two cycles of induction CT with cisplatin (75 mg/m^2) and docetaxel (75 mg/m^2) every 3 weeks. Patients with a tumor response or stabilization continued to receive cisplatin (80 mg/m^2) and oral vinorelbine (40 mg/m^2) on days 1 and 8 for two cycles, with concomitant thoracic RT (2 Gy/d, 5 d/wk, and total dose 66 Gy).

Results: Fifty-six patients were enrolled. All patients (n = 38) who received CT-RT were assessable for the tumor response. There were no complete responses. In the intent-to-treat analysis, the response rates were 32.1% after induction CT and 41.1% after CT-RT. The median progression-free and overall survival times were 9.2 months (95% confidence interval: 7–14) and 20.8 months (95% confidence interval: 13.7–24.1), respectively. Adverse effects of RT-CT were grades 3 to 4 neutropenia (four patients) and grade 3 esophageal toxicity (one patient). No treatment-related deaths occurred.

Conclusion: The oral vinorelbine-cisplatin combination with concurrent RT is feasible and has a favorable risk-benefit ratio in stage IIIA/IIIB NSCLC.

Key Words: MeSH, Lung neoplasms, Chemoradiotherapy, Oral vinorelbine.

(*J Thorac Oncol.* 2011;6: 351–357)

Non-small cell lung cancer (NSCLC) is locally advanced (stages IIIA and IIIB) at diagnosis in approximately one third of cases. These patients form a highly heterogeneous group with respect to their clinical status and prognosis. Apart from a few particular cases in which surgery can be envisaged either immediately or after neoadjuvant therapy, the standard treatment is a combination of radiotherapy (RT) and chemotherapy (CT).[1,2] Two recent meta-analyses confirmed the superiority of combined RT-CT over thoracic irradiation alone, with a 5-year survival advantage of 1.7% with sequential treatment and 2.2% with concurrent treatment.[3] Concurrent RT-CT seems to be superior to sequential treatment, with a survival advantage of approximately 6.6% at 3 years.[4] This advantage seems to be due mainly to better local tumor control leading to fewer locoregional recurrences but is somewhat offset by more esophageal toxicity.

Induction CT before concurrent treatment has not been shown to provide a further survival gain,[5] but it has the theoretical advantages of reducing the tumor volume before concurrent RT-CT and providing better control of micrometastases. It also represents an active treatment pending RT.

In this study, we evaluated induction therapy with docetaxel-cisplatin, a standard combination used in stage IV NSCLC.[6–8] The Groupe Français de Pneumo-Cancérologie (GFPC) has previously reported a phase II trial of cisplatin-

*Institut de Cancérologie et Hématologie, Centre Hospitalier Universitaire Morvan, Brest; †Centre Hospitalier Universitaire de Limoges, Limoges; ‡Centre Hospitalier Universitaire de Marseille, Marseilles; §Centre Hospitalier Universitaire de Rennes, Rennes; ‖Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne; ¶CH Villefranche-sur-Saone; #Hopital D'instruction des Armées, Toulon; **Centre Hospitalier Universitaire D'Angers, D'Angers; ††Centre Hospitalier de Draguignan, Draguignan; ‡‡Centre Hospitalier D'Antibes, D'Antibes; §§Centre Hospitalier de Lyon-Sud, Lyon; ‖‖Centre Hospitalier de Créteil, Créteil; ¶¶Centre Hospitalier de Carleville-Mézières, Carleville-Mézières, France.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Dr. Renaud Descourt, Institut de cancérologie et hématologie, Centre Hospitalier Universitaire Morvan, 5 avenue Foch, 29609 Brest CEDEX, France. E-mail: renaud.descourt@chu-brest.fr

Presented in part at the 12th World Conference on Lung Cancer, Seoul, 2007.

ISSN: 1556-0864/11/0602-0351

navelbine induction therapy before concurrent docetaxel-RT.[9] The observed efficacy and tolerability of this schedule justified a trial of a dual-agent combination for both induction and concurrent CT-RT. The cisplatin-vinorelbine combination seems to offer the best tolerability profile, while having similar efficacy to other cytotoxic combinations given concurrently with RT.[10] At equivalent doses based on bioavailability studies, oral vinorelbine has shown similar tumor response and patient survival rates to intravenous vinorelbine in previously untreated advanced-stage NSCLC.[11,12] When combined with cisplatin, oral vinorelbine was also effective for first-line treatment of metastatic disease, showing similar efficacy to a standard cisplatin-docetaxel combination.[13] In locally advanced disease, a recent international trial demonstrated the efficacy and acceptable tolerability of oral vinorelbine administered during concurrent RT.[14]

To verify the efficacy and tolerability of the oral vinorelbine and cisplatin combination with concomitant RT after cisplatin-docetaxel induction CT for locally advanced NSCLC, we conducted a phase II, multicenter trial. The main endpoint was the response rate. Secondary endpoints were the time to progression, median overall survival, and tolerability.

PATIENTS AND METHODS

Patient Selection

The main inclusion criteria were as follows: cytologically or histologically proven NSCLC, inoperable stage IIIA N2 or stage IIIB, the possibility of including all target sites in the same radiation field, at least one measurable target, Eastern Cooperative Oncology Group performance status $\leq$1, weight loss less than 10%, age between 18 and 70 years, no previous CT or RT, life expectancy more than 12 weeks, normal hepatic function (bilirubin $<$ upper limit of normal [ULN], SGOT, and/or SGPT $<$2.5 ULN), normal renal function (creatinemia $\leq$ ULN and creatinine clearance $\geq$60 ml/min), normal hematologic function (PN $>1.5 \times 10^9$/liter, platelets $>100 \times 10^9$/liter and hemoglobin $>$9.5 g/dl), satisfactory respiratory function (forced expiratory volume in 1 second $\geq$40% theoretical and $Pa_{O_2} \geq$60 mm Hg), and written informed consent.

The main exclusion criteria were unstable heart disease necessitating treatment (congestive heart failure, effort angina, significant arrhythmia, or history of myocardial infarction $<$12 months previously), psychiatric or neurologic disorders, uncontrolled infection, peripheral neuropathy grade more than 2, definitive contraindications to steroids, allergy to Polysorbate 80, another past or current malignancy, except for basocellular skin cancer, treated in situ cervical carcinoma, or any other malignancy treated with surgery alone, without relapse for at least 5 years, and catheterized pleural effusion (regardless of abundance, even in case of negative cytology).

The pretreatment extension workup consisted of abdominal and thoracic CT, cerebral CT, bone scintigraphy (or bone radiography), and bronchial endoscopy. (Routine PET scan was not required, as the trial started before this examination entered widespread use.)

Treatments

Induction CT

Induction CT consisted of two cycles of cisplatin 75 mg/m^2 and docetaxel (Taxotere) 75 mg/m^2 given on days 1 and 22 (21-day cycles). The cisplatin and docetaxel doses could be adjusted according to the results of weekly hematologic tests. Cisplatin and docetaxel could not be administered if the neutrophil count was below 1500/mm^3 or the platelet count below 100,000/mm^3. In this case, the treatment was postponed for a week. Growth factors could be given curatively or as secondary prevention for febrile neutropenia. The dose could also be adjusted according to the nadir, in case of peripheral neuropathy or renal or hepatic toxicity.

Concurrent Radio-CT

Chemotherapy. The CT regimen consisted of two cycles of cisplatin (80 mg/m^2, days 1 and 21) and oral vinorelbine (40 mg/m^2, days 1, 8, 21, and 28) with day 1 as the first day of RT. The doses were adjusted according to hematologic and nonhematologic toxicity. The dose of oral vinorelbine was halved if the neutrophil or platelet count was between 1000 and 1500/mm^3 or between 75,000 and 100,000/mm^3, respectively. Treatment was postponed for 8 days if the neutrophil count was below 1000/mm^3 or the platelet count below 75,000/mm^3. If treatment had to be postponed twice, the patient and his/her physician decided whether continued treatment was warranted.

Radiotherapy. RT began at least 15 days and no more than 3 weeks after the planned end date of cisplatin-docetaxel induction CT. The target was restricted to the macroscopic tumor volume and involved nodes. The homolateral supraclavicular fossa was treated to 60 Gy, only in patients with a tumor of the upper lobe or with upper mediastinal involvement.

The 3D dosimetry was always used, with correction for heterogeneity and calculation of dose-volume histograms (planned tumor volume [PTV], lung, marrow, etc.). The radiation dose was prescribed to the 100% isodose, and the PTV had to receive at least 95% of the prescribed dose, following International Commission on Radiation Units and Measurement recommendations.[15] The PTV was defined as the clinical tumor volume (CTV) plus a safety margin of approximately 10 to 15 mm. The total dose was 66 Gy, delivered in 33 fractions over 6½ weeks. To limit the risk of grade $\geq$3 radiation-induced pneumonitis, the total lung volume receiving 20 Gy had to be less than 30%.[16] Spinal cord dose was kept below 45 Gy.

RT was monitored by weekly gammagraphic verification or portal imaging. Medical treatment for esophagitis started at grade 1. If grade 3 acute esophagitis occurred, irradiation was suspended until symptoms subsided to level 1 of the Radiation Therapy Oncology Group (RTOG) scale. If irradiation had to be interrupted for more than 15 days, the patient and

his/her physician decided whether continued treatment was warranted.

Response and Safety

The tumor response was assessed by a central independent panel of oncologists, at the end of induction CT, and 4 weeks after concurrent radio-CT. Complete and partial responses, stabilization, and progression were defined using RECIST criteria.[17] Patients who progressed after induction CT left the study, and their subsequent treatment was managed by the investigator. Patients with a tumor response or stabilization received the concurrent radio-CT. After the end of the treatment, the patients were seen every 3 months for a physical examination and chest radiograph, plus any other examinations the investigator considered necessary. All responses had to be confirmed at least 1 month later and also had to be reviewed and confirmed by the independent panel. Safety was assessed using the National Cancer Institute Common Toxicity Criteria (2000)[18] for CT and the RTOG-European Organization for Treatment and Research (EORTC) criteria for RT.[19]

Statistical Analysis

The required number of patients was calculated with Fleming's method,[20] as modified by Herndon.[21] To avoid continuing the trial unnecessarily, the working hypothesis were as follows: in the first study phase, the strategy was to be rejected if the objective response rate was less than 30% and was to be tested in a phase III trial if more than 60%; with a type I risk of 0.02 and a type II risk of 0.10, 15 patients had to be enrolled in this first phase. If the objective response rate was between 30% and 60%, the phase II study was to be continued. Based on the same hypothesis, a further 30 patients had to be recruited, for a total of 45 patients. This approach avoids the need for a randomized phase II trial.[22] To ensure that the strategy was not excessively toxic, we planned an interim analysis of the results for the first 10 patients who received chemo-RT after induction CT. Toxicity would be considered unacceptable if four or more of these 10 patients had stage ≥ III esophageal or pulmonary toxicity.

Qualitative variables are reported as frequencies and percentages and quantitative variables as the mean, median, and range. Confidence intervals (CIs) were calculated for the response rate, time to progression, and median survival time by using Statview software version 5.0. Survival was estimated with the Kaplan-Meier method, the start date being the date of inclusion.

RESULTS

Characteristics of the Patients

Between March 2006 and May 2007, 60 patients were selected by 20 centers. Four patients could not be enrolled: three had stage IV disease and one had a tumor too large for thoracic RT, as defined in the protocol (Figure 1).

The characteristics of the 56 eligible patients are shown in Table 1. Median age was 57.4 years, and 87% of the patients were men. Performance status was 0 in 64.3% of cases, and the most frequent histologic type was adenocarcinoma (50%).

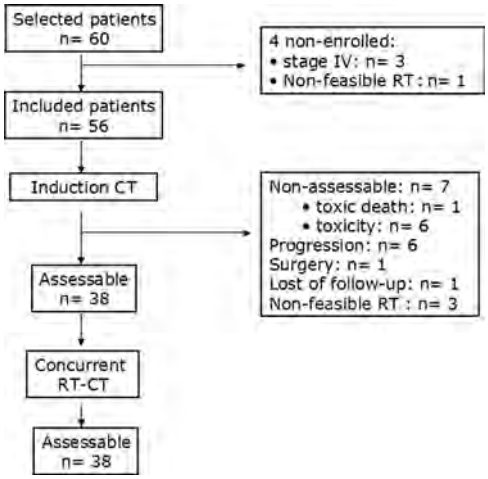

FIGURE 1. Trial flow chart. *n*, number; CT, chemotherapy; RT, radiotherapy; RT-CT, radiochemotherapy.

TABLE 1. Characteristics of the Patients ($n = 56$)

	n	Percentage
Patients included	56	
Age (±SD)	57.4 (±7.9)	
Sex (%)		
Men	49	87.5
Women	7	12.5
PS (%)		
0	36	64.3
1	20	35.7
Histology		
Squamous cell	18	32.1
Adenocarcinoma	28	50.0
Large cell	10	17.9
Stages		
IIIA	21	37.5
IIIB	35	62.5
Assessable for induction CT	49	87.5
Assessable for RT-CT	38	67.8

RT, radiotherapy; CT, chemotherapy; PS, performance status.

At the end of induction CT, seven patients were not assessable for the tumor response (six because of toxicity and one death unrelated to the study treatment). Six assessable patients progressed, one patient was able to have surgery, and one patient switched centers. Among the patients with tumor stabilization, three did not receive RT as defined in the protocol (inappropriate dose or treatment interval). Thus, 38 of the initial 56 patients were able to receive concurrent chemo-RT, all of whom were assessable for tumor response.

Dose Intensities

During the induction phase, the total doses of cisplatin and docetaxel actually received were 135 ± 11.9 mg and 135 ± 15.9 mg, respectively, corresponding to dose intensi-

TABLE 2. Dose Intensity

	Induction CT (n = 56)		Concomitant RT-CT (n = 38)	
	Mean ± SD	95% CI	Mean ± SD	95% CI
Total number of cycles	102	—	73	—
Mean number of cycles/patient	1.80 ± 0.39	1.70–1.9	1.90 ± 0.27	1.80–2.0
Dose intensity (mg)				
Cisplatin	135 ± 11.9	133–138	141 ± 19.1	137–146
Docetaxel	135 ± 15.6	132–138	—	—
Oral vinorelbine	—	—	137 ± 28.0	130–143
Mean relative dose intensity (%)				
Cisplatin	98.4 ± 5.22	97–99.4	94.3 ± 13.75	91.2–97.5
Docetaxel	99.0 ± 2.40	98.6–99.5	—	—
Oral vinorelbine	—	—	95.3 ± 14.42	92.0–98.6
RT				
Total dose (Gy)	—	—	64.6 ± 4.53	63.1–66
Number of fractions	—	—	33.2 ± 1.90	32.6–33.8
Observance (%)	—	—	97.84 ± 6.86	95.6–100

RT, radiotherapy; CT, chemotherapy.

ties of 98.4% (±5.22) for cisplatin and 99% (±2.40) for docetaxel (Table 2). During the chemo-RT phase, the respective doses of cisplatin and oral vinorelbine were 141 ± 19.1 mg and 137 ± 28 mg, corresponding to dose intensities of 94.3% (±13.7) and 95.3% (±14.4). The total number of CT cycles was 1.8 ± 0.40 and 1.9 ± 0.27 for the induction and concurrent treatment phases, respectively. The mean dose of radiation received was 64.6 ± 4.53 Gy (95% CI: 63.1–66.0).

Safety

During the induction phase, the main toxicity was hematologic, with grades 3 to 4 neutropenia in 28.6% of cases and febrile neutropenia in less than 5%. One death unrelated to the treatment (because of cardiogenic shock) occurred during this phase. Six patients experienced severe toxicity (grade ≥3), ruling out further study treatment, and consisting of infections in three cases, and renal failure, docetaxel hypersensitivity, and heart failure in one case each.

Among the 38 patients who received chemo-RT, four experienced grades 3 to 4 neutropenia, associated with fever in two cases. Regarding nonhematologic toxicity (Table 3), 15 patients had symptoms of esophagitis (13 grade 2 and two grade 3). Only one patient had grade 2 pulmonary toxicity (radio-induced pneumonitis). One patient experienced grade 3 peripheral neuropathy. There were no treatment-related deaths. Late-onset grades 3 to 4 adverse effects consisted of esophageal stenosis in two patients and radiation-induced pulmonary fibrosis of the right upper lobe in one patient (Table 3).

Efficacy

No complete responses were obtained after induction CT or chemo-RT (Table 4). Partial responses were observed in 18 (32%) patients after induction CT and in 23 (41.1%) patients after chemo-RT. Among the 38 patients who were able to receive the full study treatment, the objective response rate was 60.5%.

The first evaluation after concurrent chemo-RT showed tumor progression in seven patients: it was locoregional in two cases (including one with neoplastic pericarditis) and distant in five cases (brain in two patients, adrenal in one patient, bone and adrenal in one patient, and bone in one patient).

The last survival analysis was done on June 30, 2010. In the intent-to-treat analysis, the median progression-free survival

TABLE 3. Nonhematological Toxicity

	Grade 2		Grade 3		Grade 4	
	n	Percentage	n	Percentage	n	Percentage
Induction CT (n = 56)						
Alopecia	13	23.2	—	—	—	—
Asthenia	1	1.8	—	—	—	—
Pain	2	3.6	2	3.6	—	—
Docetaxel hypersensitivity	—	—	—	—	1	1.8
Deep vein thrombosis	—	—	1	1.8	—	—
Renal failure	4	7.1	1	1.8	1	1.8
Infectious disease	3	5.3	3	5.3	—	—
Pneumonia	4	7.1	—	—	—	—
Arrhythmia. Cardiac failure	2	3.6	1	1.8	—	—
Nausea, vomiting	7	12.5	—	—	—	—
Concurrent RT-CT (n = 38)						
Nausea, vomiting	4	10.5	1	2.6	—	—
Esophagitis	13	34.2	2	5.3	—	—
Jugular vein thrombosis	1	2.6	—	—	—	—
Pneumonia	1	2.6	—	—	—	—
Radiation pneumonitis	1	2.6	—	—	—	—
Radiation induced pulmonary fibrosis	—	—	—	—	1	2.6
Esophageal stenosis	2	5.3	1	2.6	1	2.6
Peripheral neuropathy	—	—	1	2.6	—	—
Asthenia	4	10.5	1	2.6	—	—

RT, radiotherapy; CT, chemotherapy.

TABLE 4. Overall Response Rate and Survival (Intent-to-Treat Analysis)

	After Induction CT	After Concomitant RT-CT
Patients	56	56
Response		
PR	18 (32.1%)	23 (41.1%)
SD	25 (44.6%)	8 (14.3%)
PD	6 (10.7%)	7 (12.5%)
DCR	43 (76.7%)	31 (55.4%)
NA	7 (12.5%)	18 (32.1%)
Survival (mo)		
Progression-free survival (mo)	9.2 (95% CI: 7–14)	
Overall survival	20.8 (95% CI: 13.7–24)	

PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; NA, nonassessable; RT, radiotherapy; CT, chemotherapy.

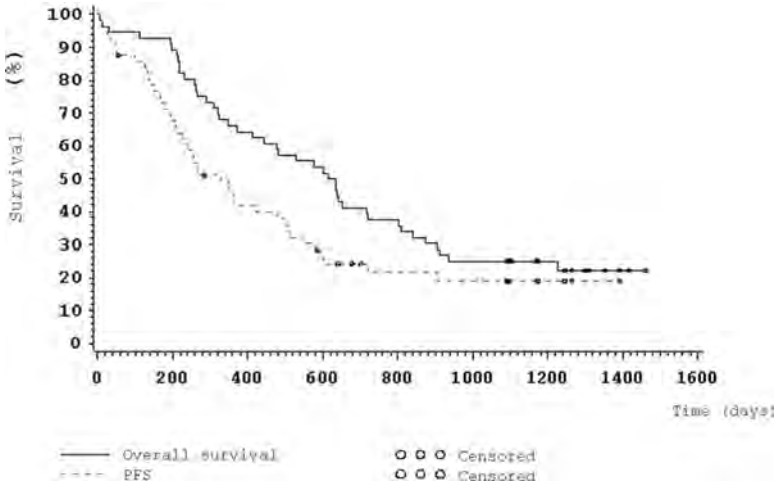

FIGURE 2. Progression-free survival and overall survival (intent-to-treat analysis).

time was 9.2 months (95% CI: 7–14), and the median overall survival time was 20.8 months (95% CI: 13.7–24.1) (Figure 2). The survival rates at 1 and 2 years were 66.1% (95% CI: 52.1–76.8) and 37.1% (95% CI: 23.3–50.9), respectively.

DISCUSSION

In patients with locally advanced NSCLC, two cycles of the cisplatin-docetaxel combination, followed by concurrent chemo-RT with cisplatin and oral vinorelbine, yielded an overall tumor response rate of 41.1% in the intent-to-treat analysis. The updated median survival time is 20.8 months, with 1-year and 2-year survival rates of 66.1% and 37.1%, respectively. In a recent phase II trial, the same cisplatin-oral vinorelbine combination was used both for induction and for concomitant chemo-RT.[14] The median survival time was similar to that obtained in this study (~23 months), and the 1-year and 2-year survival rates were 74% and 48%, respectively. In contrast, the overall response rate was higher (53% in the intent-to-treat analysis), and there was one complete response. This difference in response rates could be explained by the fact that all responses observed in our study were reviewed by an independent expert panel, contrary to the study by Krzakowski et al.[14] Elsewhere, in a phase II study conducted by our group (GFPC) and using the same method of evaluation, Vergnenégre et al.[9] reported very similar response rates to those observed in this study. This latter study used identical induction CT but single-agent docetaxel for concurrent chemo-RT. The results of this study are also in keeping with other recent reports.[23–26] Using cisplatin-vinorelbine induction with a concomitant RT started on day 4 of cycle 2, Zatloukal et al.[23] obtained a median overall survival time of 16.6 months and a progression-free survival time of 11.9 months. Using an induction by two cycles of docetaxel 75 mg/m^2 on day 1 and cisplatin 40 mg/m^2 on days 1 and 2, followed by concurrent CT-RT with weekly docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2, Senan et al.[24] obtained a 1-year survival rate of 63.2%, with good tolerability. In another study[25] using the same combination for induction but at different doses (docetaxel 40 mg/m^2 and cisplatin 40 mg/m^2 on days 1, 8, 29, and 36), the median progression-free and median survival times were 13.4 and 26.8 months, respectively. Finally, with an induction consisting of 3 weekly cycles of paclitaxel 100 mg/m^2 and carboplatin area under the curve 2, followed by 6 weekly cycles of paclitaxel 60 mg/m^2 and carboplatin area under the curve 2 combined with thoracic RT, Tell et al.[26] obtained in 64 patients a time to progression and a median overall survival of 8.2 and 15.3 months, respectively.

The somewhat modest tumor response rate obtained in our study contrasts with the patients' relatively good overall survival. Nevertheless, our overall survival analysis did not take the patients' poststudy treatment into account. This is one weakness of our study. There is also a possible selection bias related to the inclusion of patients in good overall condition and to the overrepresentation of adenocarcinomatous tumors, both factors being associated with better outcome.[27]

Induction CT before concurrent treatment has not been shown to provide a further survival gain,[5] but it has the theoretical advantages of reducing the tumor volume before concurrent RT-CT and providing better control of micrometastases. It also represents an active treatment pending RT but carries a risk of delaying concurrent treatment and of inducing radioresistance. We observed a low overall response rate (32.1%) after the two cisplatin-docetaxel cycles, contrasting with the higher rates reported with the same combination in first-line advanced-stage NSCLC[6] or as induction therapy for potentially operable IIIAN2 NSCLC.[28] Another EORTC phase II trial[29] using this combination before radical treatment (surgery or RT) for locally advanced stage IIIAN2 disease (histologically proven N2) reported a modest overall response rate (39%), as in our study. The reasons for these dispregnancies are unclear. Nevertheless, this combination is highly toxic, with six cases of major toxicity and six cases of disease progression during induction therapy. More than 20% of patients might have been cured by first-line treatment. The same combination is also associated with a high risk of neutropenia.[28,29]

The choice of the cisplatin-oral vinorelbine combination and concurrent RT was based partly on the results of the CALGB 9431 study.[10] This randomized phase II trial comprised three arms, in which cisplatin was combined with paclitaxel, vinorelbine, or gemcitabine. The response and

survival rates were similar in the three arms, but tolerability was better in the cisplatin-vinorelbine arm, which seems to have the best risk-benefit ratio when used in combination with RT. The main value of the oral form lies in the better quality of life it procures, avoiding stays in CT units and the risks associated with intravenous administration; it also requires less hospitalization and lowers treatment costs.[30]

The choice of cisplatin-based CT during RT may also partly explain the comparatively good overall survival observed in our study. Two randomized phase II trials, one American[31] and the other Spanish,[32] comparing induction and consolidation, used carboplatin as the standard platinum salt. Although it is difficult to compare these studies, the median overall survival rates obtained in the induction arms were lower than in our population. In addition, a recent meta-analysis of individual data by Ardizzoni et al.[33] suggests that cisplatin is more effective than carboplatin in terms of both the response rate and overall survival.

Our results confirm the safety of the cisplatin-oral vinorelbine combination with concurrent thoracic RT. All the patients who received concurrent chemo-RT were assessable for the tumor response, and grade ≥3 toxicity was relatively infrequent. The frequency of febrile neutropenia (~5%) was acceptable. Esophagitis and radiation-induced pneumonia were also infrequent and mainly grade 2 or 3. These rates are similar to those reported in the literature with an identical combination.[14] Moreover, RT only had to be interrupted in one of our patients, who recovered within 15 days and was able to pursue the study treatment. These low complication rates were obtained even though the dose intensities of oral vinorelbine and cisplatin were near optimal. Oral vinorelbine-cisplatin should thus be preferred to other doublets and especially, cisplatin-docetaxel combination that seems to be more toxic during concomitant radiation therapy.[24] In conclusion, in patients with locally advanced NSCLC, this phase II trial shows that cisplatin-docetaxel induction therapy is highly toxic and gives only a modest tumor response rate but that oral vinorelbine cisplatin is well tolerated during concurrent RT. These results do not warrant a phase III trial.

ACKNOWLEDGMENTS

The authors thank Dr. A. Chajarra from the University Hospital of Brest.

Supported by an unrestricted educational grant from Pierre Fabre.

Administrative support was provided by Direction de la Recherche Clinique (Brest University Hospital).

Author contributions: R. Descourt and G. Robinet had full control of the study design, data analysis and interpretation, and manuscript preparation. All the authors were involved in planning the analysis and drafting the manuscript. The final draft manuscript was approved by all the authors.

REFERENCES

1. Robinson LA, Ruckdeschel JC, Wagner H Jr, et al. American College of Chest Physicians. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:243S–265S.
2. Jett JR, Schild SE, Keith RL, et al. American College of Chest Physicians. Treatment of non-small cell lung cancer, stage IIIB: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132:266S–276S.
3. Rolland E, Le Chevalier T, Auperin A, et al. Sequential radio-chemotherapy versus radiotherapy alone and concomitant RT-CT versus RT alone in locally advanced non-small-cell lung cancer: two meta-analyses using individual patient data from randomized clinical trials. *J Thorac Oncol* 2007;2:Abstract A1–04.
4. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non small cell lung cancer (NSCLC). *J Clin Oncol* 2010;28:2181–2190.
5. Vokes EE, Herndon JE, Kelley D, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III nonsmall cell lung cancer: Cancer and Leukemia Group *B. J Clin Oncol* 2007;25: 1698–1705.
6. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N Engl J Med* 2002;346:92–98.
7. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21:3016–3024.
8. Douillard JY, Laporte S, Fossella F, et al. Comparison of docetaxel- and vinca alkaloid-based chemotherapy in the first-line treatment of advanced non-small cell lung cancer: a meta-analysis of seven randomized clinical trials. *J Thorac Oncol* 2007;2:939–946.
9. Vergnenègre A, Daniel C, Lena H, et al. Docetaxel and concurrent radiotherapy after two cycles of induction chemotherapy with cisplatin and vinorelbine in patients with locally advanced non small cell lung cancer. A phase II trial conducted by the Groupe Français de Pneumo-Cancérologie (GFPC). *Lung Cancer* 2005;47:395–404.
10. Vokes EE, Herndon JE, Crawford J, et al. Randomised phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non small cell lung cancer: Cancer and Leukemia Group B Study 9431. *J Clin Oncol* 2002;20:4191–4198.
11. Jassem J, Ramlau R, Karnicka-Mlodkowska H, et al. A multicenter randomised phase II study of oral versus intravenous vinorelbine in advanced non-small-cell lung cancer patients. *Ann Oncol* 2001;12:1375–1381.
12. Marty M, Fumoleau P, Adenis A, et al. Oral vinorelbine pharmacokinetics and absolute bioavailability study in patients with solid tumors. *Ann Oncol* 2001;12:1643–1649.
13. Tan EH, Rolski J, Grodzki T, et al. Global Lung Oncology Branch trial 3 (GLOB3): final results of a randomised multinational phase III study alternating oral and i.v. vinorelbine plus cisplatin versus docetaxel plus cisplatin as first-line treatment of advanced non-small-cell lung cancer. *Ann Oncol* 2009;20:1249–1256.
14. Krzakowski M, Provencio M, Utracka-Hutka B, et al. Oral vinorelbine and cisplatin as induction chemotherapy and concomitant chemo-radiotherapy in stage III non-small cell lung cancer: final results of an international phase II trial. *J Thorac Oncol* 2008;3:994–1002.
15. International Commission on Radiation Units and measurement (ICRU). Prescribing, Recording and Reporting Photon Beam Therapy. WashingThe authors thank Dr. A. Chajarra from the University Hospital of Brest. The authors thank Dr. A. Chajarra from the University Hospital of Brest. The authors thank Dr. A. Chajarra from the University Hospital of Brest. ton, DC: ICRU, 1993.
16. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45:323–329.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–216.
18. Cancer Therapy Evaluation Program. Common Toxicity Criteria, Version 2.0, Revised March 23, 1998.
19. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
20. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. *Biometrics* 1982;38:143–151.

21. Herndon JE, 2nd. A design alternative for two-stage, phase II, multicenter cancer clinical trials. *Control Clin Trials* 1998;19:440–450.
22. Gan HK, Grothey A, Pond GR, et al. Randomized phase II trials: inevitable or inadvisable. *J Clin Oncol* 2010;28:2641–2647.
23. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004;46:87–98.
24. Senan S, Cardenal F, Vansteenkiste J, et al. A randomized phase II study comparing induction or consolidation chemotherapy with cisplatin-docetaxel, plus radical concurrent chemoradiotherapy with cisplatin-docetaxel, in patients with unresectable locally advanced non-small-cell lung cancer. *Ann Oncol* In press.
25. Segawa Y, Kiura K, Takigawa N, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. *J Clin Oncol* 2010;28:3299–3306.
26. Tell R, Sederholm C, Klintenberg C, et al. Multicentre phase II trial of paclitaxel and carboplatin with concurrent radiotherapy in locally advanced non-small cell lung cancer. *Anticancer Res* 2008;28:2851–2857.
27. Hirsch FR, Spreafico A, Novello S, et al. The prognostic and predictive role of histology in non small cell lung cancer: a literature review. *J Thorac Oncol* 2008;3:1468–1481.
28. Betticher DC, Hsu Schmitz SF, Tötsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. *J Clin Oncol* 2003;21:1752–1759.
29. Biesma B, Manegold C, Smit HJ, et al. (for the EORTC Lung Cancer Group). Docetaxel and cisplatin as induction chemotherapy in patients with pathologically-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European organization for research and treatment of cancer (EORTC 08984). *Eur J Cancer* 2006;42:1399–1406.
30. Liu G, Franssen E, Fitch MI, et al. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997;1:110–115.
31. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non small lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005;23:5883–5891.
32. Garrido P, Arellano A, Massuti B, et al. Randomized phase II trial using concomitant chemoradiation plus induction or consolidation chemotherapy for unresectable stage III non small cell lung cancer patients. Mature results of the SLCG 008 study. *J Thorac Oncol* 2007;2:S365.
33. Ardizzoni A, Boni L, Tiseo M, et al. CISCA (CISplatin versus CArboplatin). Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. Meta-analysis Group. *J Natl Cancer Inst* 2007;99:847–857.

