Sequential Chemotherapy in Nonsmall-Cell Lung Cancer

Cisplatin and Gemcitabine Followed by Docetaxel

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BACKGROUND. Improving results in nonsmall-cell lung cancer (NSCLC) will require the development of new drugs and strategies to combine available agents. On the basis of data indicating the activity of docetaxel as second-line therapy, a Phase II study was conducted to evaluate the efficacy and toxicity of the sequential combination of chemotherapy consisting of cisplatin (P) and gemcitabine (G) followed by docetaxel (DOC) in patients with advanced NSCLC.

METHODS. Patients with 1997 TNM stage IIIB (pleural effusion)/stage IV NSCLC, performance status (PS) of 0–1, and normal organ function were eligible. Therapy consisted of P at 75 mg/m^2 on Day 1 and G 1200 mg/m^2 on Days 1 and 8 every 3 weeks for 3 cycles followed, in nonprogressive patients, by DOC 30 mg/m^2 every week for 6 consecutive weeks every 8 weeks for 2 cycles.

RESULTS. Fifty-two eligible patients were enrolled (M/F, 39/13; stage IIIB/IV, 8/44; PS 0, 73%, PS 1, 27%; median age, 58 years; range, 36–73). The overall response rate was 36.5% (95% confidence interval [CI]: 23–49). The median overall survival was 11 months (95% CI: 9–13); the median progression-free survival was 6 months (95% CI: 5–7); and the 1- and 2-year survivals were 48% and 25%, respectively. One- and 2-year progression-free survivals were 12% and 8%, respectively. Both phases of the treatment protocol were well tolerated.

CONCLUSIONS. P/G followed by weekly DOC is well tolerated and active as first-line therapy for NSCLC patients and provides a feasible chemotherapeutic option in this clinical setting. ***Cancer* 2007;109:727–31.** © *2007 American Cancer Society.*

KEYWORDS: sequential chemotherapy, nonsmall-cell lung cancer, NSCLC.

Lung cancer is the leading cause of cancer-related death worldwide and approximately 80% of all cases are categorized as nonsmall-cell lung cancer (NSCLC).[1] Chemotherapy with platinum-based doublets is the mainstay in the management of advanced NSCLC and has been shown to provide a modest but significant survival benefit with an improvement in quality of life, as compared with best supportive care.[2] In this context, cisplatin-based regimens appear to be more active than carboplatin-based ones, as demonstrated by a recently conducted individual patient meta-analysis of randomized trials.[3] Unfortunately, cisplatin-based regimens have the disadvantage of cumulative toxicity requiring reduction in individual drug dosages and limiting the number of cycles that may be delivered. To avoid increased toxicity with continued treatment, therapeutic strategies using a limited number of chemotherapy cycles have been devised. Two randomized studies have indeed compared fixed numbers of chemotherapy cycles (3 cycles of the mitomycin C plus vindesine plus cisplatin [MVP] regimen and 4 cycles

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of carboplatin/paclitaxel) vs continued treatment (up to 6 cycles with MVP and until progression with carboplatin/paclitaxel): although no statistically significant difference in terms of response and survival was found in either study, a trend toward better efficacy for continued treatment was observed in both studies, despite increased cumulative toxicity, such as peripheral neurotoxicity, fatigue, and anemia. In addition, both studies were underpowered to truly demonstrate the noninferiority of the strategy using a limited number of treatment cycles.[4,5] An alternative strategy to reduce cumulative toxic effects while preserving activity could be the administration of a limited number platinum-based chemotherapy cycles followed by maintenance/sequential therapy with nonplatinum agents. This strategy was recently explored by Novello et al[6] in a Phase III study in which patients received 2 cycles of cisplatin and gemcitabine and were subsequently randomized between 3 additional cycles of the same combination or gemcitabine alone. Although preliminary, the results of that study suggest that maintenance with single-agent gemcitabine is equally effective, as compared with continuing cisplatin, and has a significantly more favorable toxicity profile in terms of both hematologic and nonhematologic toxicity.[6] Along these lines, promising results were recently presented by Belani et al[7,8] suggesting that weekly paclitaxel maintenance after 6 cycles of carboplatin/paclitaxel may indeed prolong survival with minimal additional toxicity. Similar results were obtained by Brodowicz et al[9] with gemcitabine maintenance therapy after initial therapy with gemcitabine plus cisplatin. Maintenance chemotherapy was feasible and produced significantly longer time to progression compared with best supportive care alone. Whereas the former study suggests that altering the schedule of paclitaxel in the maintenance phase may somehow overcome or delay the emergence of resistance, an alternative strategy could be to sequentially administer non-cross-resistant drugs after a limited number of a platinum-based doublet, thereby increasing drug diversity, and possibly antitumor activity, while decreasing platinum-related cumulative toxicity. In this context in vitro biological evidence and recent clinical data demonstrate that taxanes have activity in patients with platinum-resistant NSCLC and improve survival as compared with supportive care or other chemotherapy regimens when given as second-line therapy.[10–15]

Based on these data, we conducted a Phase II study to evaluate the tolerability and activity of a sequential strategy using weekly docetaxel (DOC) given after 3 cycles of cisplatin (P) and gemcitabine (G) as first-line treatment in patients with locally advanced, unresectable, or metastatic NSCLC. The choice of a weekly schedule of DOC was based on a meta-analysis recently conducted by our group demonstrating that weekly administration schedules significantly improve the tolerability while preserving the activity of DOC when given as second-line therapy.[16]

MATERIALS AND METHODS

Inclusion Criteria

Eligibility criteria included histologically or cytologically documented advanced NSCLC (1997 TNM stage IIIB or stage IV disease), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1, and adequate hematologic (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin ≥ 10 g/dL), hepatic (serum bilirubin and transaminases less than twice the upper limit of normal), and renal (serum creatinine ≤ 1.5 mg/dL or a calculated creatinine clearance ≥ 60 mL/min) function. Asymptomatic brain metastases not requiring immediate radiation therapy or adequately treated brain metastases were allowed. Other eligibility criteria were the presence of at least 1 unirradiated and bidimensionally measurable lesion. Previous surgery and radiation therapy were acceptable. No prior chemotherapy or biologic therapy were allowed. All patients gave written informed consent before study entry. The study was approved by the local ethics committees and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the guidelines on good clinical practice.

Pretreatment Evaluation and Treatment

At baseline all patients had a complete history and physical examination, complete blood work-up, electrocardiogram, and a computer tomography scan of the chest, brain, upper abdomen, and any other sites of known disease. Other scans were performed if clinically indicated. Treatment consisted of 3 cycles of P and G every 21 days. P was administered intravenously at 75 mg/m^2 on Day 1, with appropriate hydration and antiemetics; G was administered on Days 1 and 8 at 1200 mg/m^2. After restaging, nonprogressive patients received single-agent DOC at a dose of 30 mg/m^2 every week for 6 consecutive weeks every 8 weeks. Two cycles of docetaxel were planned. Dose modifications for the cytotoxic agents were performed during the course of treatment for significant hematologic and nonhematologic toxicity. Briefly, an absolute neutrophil count greater than $\geq 1.5 \times 10^9$/L and platelet count greater than 100×10^9/L were required before each cycle of therapy. After grade 4

TABLE 1
Pretreatment Patient Characteristics

No. of patients	52
Median age, y [range]	58 [36–73]
Sex	
Men	39 (75%)
Women	13 (25%)
Tumor histology	
Adenocarcinoma	28 (54%)
Squamous cell	8 (15%)
Large cell	11 (21%)
Undifferentiated lung cancer NSC	5 (10%)
Stage at diagnosis	
IIIB	8 (15%)
IV	44 (85%)
ECOG performance status	
0	38 (73%)
1	14 (27%)
Metastatic sites	
Bone	17 (38.6%)
Lymph nodes	14 (31.8%)
Brain	9 (20.4%)
Adrenal	8 (18.1%)
Liver	5 (11.3%)
1 metastatic site	17 (39%)
2 metastatic sites	15 (34%)
≥3	12 (27%)

neutropenia lasting more than 7 days or grade 4 febrile neutropenia or grade 4 thrombocytopenia, patients were retreated with a dose reduction of 25% after recovery. Toxicities were graded according to the World Health Organization (WHO) toxicity criteria. Therapy was discontinued and the patient removed from protocol in the presence of progressive disease (PD), unacceptable toxicity as assessed by the investigator, or upon patient request.

Statistical Methods

The primary objective of this trial was to evaluate the activity in terms of objective response rate of the P/G followed by DOC sequence treatment. Secondary endpoints were the evaluation of safety profile (acute, chronic, and delayed toxicities), time to progression, and survival. The study was therefore designed as a Phase II trial according to the method described by A'Hern.[17] A sample size of 52 patients was considered sufficient to give an 80% probability of rejecting a baseline response rate of 20% with an exact 1% 1-sided significance test when the true response rate was 40%. The drug regimen should have been considered for further studies if at least 18 responses to the sequential treatment were observed. All patients enrolled were considered in the intention-to-treat population (ITT) evaluated for the efficacy and safety analysis.

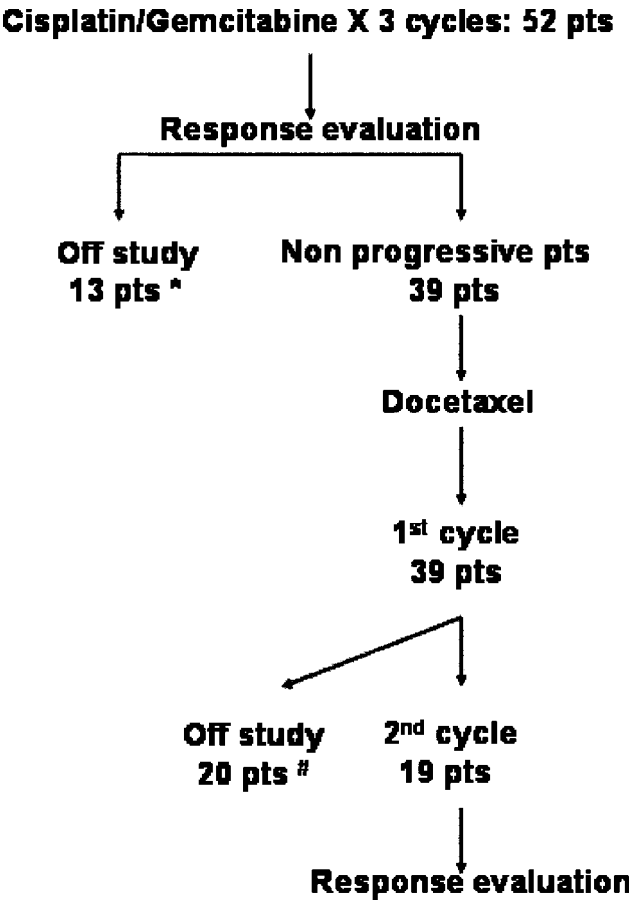

FIGURE 1. Study design. *PD, 10 patients; Refusal, 2 patients; Other, 1 patient. #PD, 17 patients; RT, 3 patients.

The time to event analysis was performed according to the Kaplan-Meier method.

RESULTS

Patient Characteristics

Fifty-two eligible patients with advanced NSCLC were enrolled in the study (Table 1). Thirty-nine (75%) were men and 13 (25%) were women, with a median age of 58 years (range, 36–73 years). Forty-four (85%) patients had stage IV disease and 8 (15%) patients had stage IIIB disease. Thirty-eight (73%) patients had an ECOG PS of 0 and 14 (27%) had an ECOG PS of 1. Twenty-eight patients had adenocarcinoma, 8 had squamous cell carcinoma, 11 had large-cell carcinoma, and 5 had undifferentiated lung cancer nonsmall-cell carcinoma. All 52 patients received 3 cycles of P/G; of these, 13 patients went off protocol before the DOC cycle because of PD (10 patients), informed consent withdrawal (2 patients), and treatment delay more than 3 weeks because of severe disphagia (1 patient). Thirty-nine patients went on

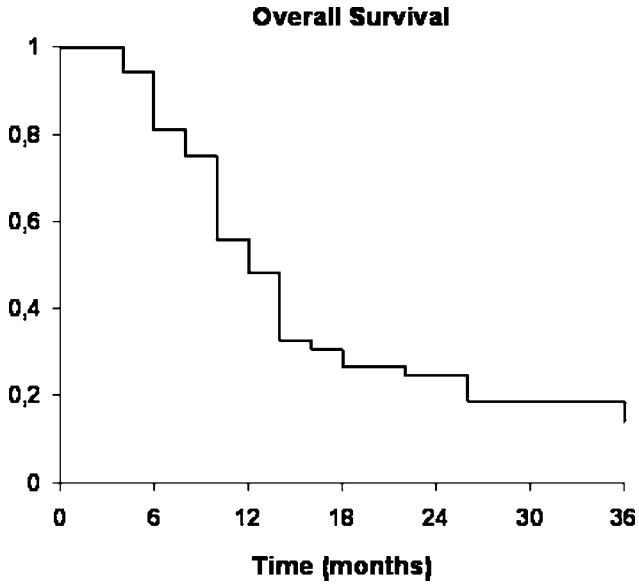

FIGURE 2. Survival analysis: intent to treat (Kaplan-Meier curve).

to receive weekly DOC, of whom 19 completed 2 planned cycles (Fig. 1). Reasons for treatment discontinuation other than PD were radiotherapy treatment in 3 stage IIIB patients.

Response and Survival

Of the 52 patients who received P/G, 2 (3.9%) experienced a complete response (CR), 15 (28.8%) a partial response (PR) with a relative risk (RR) of 32.7% (95% confidence interval [CI]: 19–45), 25 (48%) patients had stable disease, and 10 (19.3%) patients experienced PD. During the weekly DOC phase, 6 patients who had had an objective response to P/G experienced further improvement, 4 patients maintained the response, and 4 patients progressed. Similarly, 2 patients with stable disease to P/G had further tumor shrinkage that reached the criteria for PR, 12 patients remained stable, and 11 patients progressed. The overall response rate (ORR) to the entire sequential treatment was 36.5% (95% CI: 23–49). Median response duration was 7 months (range, 4–25 months). Figure 2 illustrates the Kaplan-Meier survival curve for all 52 patients. The median overall survival was 11 months (95% CI: 9–13); the median progression-free survival was 6 months (95% CI: 5–7); and the 1- and 2-year survivals were 48% and 25%, respectively. One- and 2-year progression-free survivals were 12% and 8%, respectively.

Toxicity

A total of 156 cycles of P/G and 328 weekly doses of DOC were administered. The median number of weeks of DOC received was 6. Both phases of the treatment protocol were well tolerated and there were no toxic deaths. Six (11.5%) patients underwent a dose modification almost entirely due to myelosuppression during the P/G phase, whereas no dose reductions or delays were necessary during the weekly administration of DOC. We observed mainly hematologic toxicities. In the first phase 8 patients experienced grade 3–4 neutropenia (15.3%) and 1 patient had grade 3 thrombocytopenia (1.9%); only 2 patients (3.8%) experienced grade 3 febrile neutropenia. In the DOC phase only 1 patient experienced grade 3 neutropenia. Nonhematologic toxicities were relatively uncommon and moderate in both phases. Peripheral neurotoxicity, nail changes, or conjunctivitis were not observed with weekly administration of DOC. Reversible allergic reactions were observed in 2 patients after DOC administration and did not require treatment discontinuation.

DISCUSSION

Our results demonstrate the feasibility and tolerability of a sequential strategy with P/G followed by weekly DOC as first-line treatment of patients with advanced NSCLC. The rationale for such an approach is that tumor resistance to a given combination of cytotoxic drugs would be circumvented by the sequential use of a third drug and the cumulative toxicity associated with the prolonged administration of a platinum-containing doublet or with the simultaneous combination of more than 2 drugs would be avoided. The safety profile of our regimen is comparably better than other Phase II-III trials using conventional doublets in which a high rate of severe neutropenia, thrombocytopenia, anemia, renal toxicity, and neuropathy is reported.[18–20] This issue is of particular importance given the palliative nature of treatment. In our study there were no treatment-related deaths. Grade 3–4 neutropenia was observed in 15.3% of the patients receiving P/G, with only 2 patients experiencing grade 3 febrile neutropenia. Furthermore, in the first phase of the present study the incidence of grade 3 thrombocytopenia was 1.9%. Peripheral neurotoxicity, nail changes, or conjunctivitis were not observed with weekly administration of docetaxel. Thus, as observed in the DISTAL-1 randomized Phase III trial, as well as in a recent meta-analysis, weekly scheduling of docetaxel remarkably reduces myelotoxicity in pretreated NSCLC patients without decreasing antitumoral activity.[16,21]

In our study 85% of the patients were at stage IV and 61% had 2 or more sites of distant metastasis. The antitumor activity was within the expected range,

with a best overall RR of 36.5%, a median survival time of 11 months, and a 1-year survival rate of 48%. Nine of the patients at stage IV had brain metastasis and a median progression-free survival of 6 months (95% CI: 5–7) and an overall survival of 10 months (CI: 95% 6–14) for these patients were reported. It should be pointed out that because 3 of them attained a PR and 1 a CR, systemic chemotherapy may produce responses in brain lesions.

In conclusion, while waiting for a tailored, more rational approach to lung cancer treatment, whether evaluating EGFR mutations or the level of the excision repair cross-complementing 1 (ERCC1) gene, empirical strategies using chemotherapeutic drugs are still a reasonable alternative. In this context, the sequential regimen consisting of P/G followed by weekly DOC appears to have a favorable cost-benefit ratio in terms of extremely manageable toxicity (especially with regard to cumulative neurotoxicity) and activity and could therefore be considered for further evaluation.

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