Randomized Phase II Trial of Sequential Chemotherapy in Advanced Non-Small Cell Lung Cancer (SWOG 9806): Carboplatin/Gemcitabine followed by Paclitaxel or Cisplatin/Vinorelbine followed by Docetaxel

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ABSTRACT

Purpose: Improving chemotherapeutic efficacy in non-small cell lung cancer (NSCLC) will require the development of new drugs or new strategies to better use currently available agents. Sequential administration offers an opportunity to increase drug diversity while maintaining dose intensity. On the basis of the data indicating the activity of taxanes as second-line therapy and the lack of efficacy for more than three cycles of platinum-based therapy, this randomized Phase II study tested the concept of planned sequential chemotherapy in advanced NSCLC.

Experimental Design: Patients with selected stage IIIb (pleural effusion)/stage IV NSCLC, performance status of 0–1 and normal organ function were eligible. Therapy: arm 1, carboplatin (area under the curve = 5.5 mg/ml × min day

INTRODUCTION

Of 160,000 patients who develop non-small cell lung cancer (NSCLC) in the United States in the next year, at least 40% will present with metastatic disease, and the vast majority of the remainder (>80%) will eventually develop metastases. Recent advances in chemotherapy have improved the outlook for patients with stage IV disease. In S9308, the Southwest Oncology Group (SWOG) demonstrated the superiority of cisplatin/vinorelbine versus single-agent cisplatin, with median survivals of 8 and 6 months, respectively (1–3). Subsequently, S9509 demonstrated the similar median and landmark survival for regimens of carboplatin/paclitaxel and cisplatin/vinorelbine. The recent results of the Eastern Cooperative Oncology Group Trial 1594 also demonstrated similar degrees of response and survival for four current platinum-based regimens (4). Similar findings from several other trials indicate that a plateau in efficacy has been reached with two drug regimens, which has led to evaluation of three drug regimens. Combinations in which the drugs are administered concurrently are most commonly used but have the disadvantage of additive toxicity, requiring that individual drug dosages be reduced (5). Sequential administration of chemotherapeutic agents or regimens has the advantage of eliminating additive toxicity and permits delivery of full dosages of each individual drug. Mathematical modeling, in vitro biological evidence, and recent clinical trials also indicate that planned sequential administration of chemotherapy regimens before the emergence of clinical resistance may be advantageous (6).

Pilot studies at Loyola University (7) and University of California, Davis (8), indicated the feasibility and promising activity of the sequential regimens tested in S9806. While awaiting maturation of S9509 a randomized Phase II trial of these two...
regimens was conducted to evaluate their tolerability and activity in the cooperative group setting. If one or both regimens were demonstrated to be promising, then a randomized Phase III trial would be proposed comparing sequential therapy to a standard two drug regimen.

PATIENTS AND METHODS

Inclusion Criteria. Patients with histologically documented advanced (stage IIIb: pleural effusion or multiple lesions in a lobe containing a $T_3$ or $T_4$ primary/stage IV) NSCLC were eligible. A performance status of 0–1 and acceptable renal (calculated creatinine clearance of $>50$ ml/min), hepatic (serum bilirubin and transaminases less than twice the upper limit of normal), and hematological function (absolute neutrophil count $\geq 1800$/ml, platelets $\geq 100,000$/ml, hemoglobin $\geq 10$ g/dl) were required. The study was approved by the Institutional Review Boards of the respective institutions, and all patients gave written informed consent.

Treatment. Patients were randomized to receive either carboplatin/gemcitabine followed by paclitaxel (arm 1) or cisplatin/vinorelbine followed by docetaxel (arm 2). Randomization was centrally performed at the SWOG statistical center. Patients on arm 1 received carboplatin area under the curve $=5.5$ mg/ml $\times$ min day 1 with gemcitabine (1000 mg/m$^2$ days 1 and 8). Therapy was repeated every 21 days for three cycles. After three cycles of gemcitabine/carboplatin, all patients, including those achieving a response (complete remission, partial response), stable disease, or progressive disease received sequential therapy with single-agent paclitaxel at 225 mg/m$^2$ administered over 3 h every 21 days for three cycles. Patients on arm 2 received cisplatin (100 mg/m$^2$ day 1) and vinorelbine (25 mg/m$^2$ days 1 and 8 every 21 days) for three cycles. After three cycles of cisplatin/vinorelbine, all patients, including those achieving a response (complete remission, partial response), stable disease, or progressive disease received sequential therapy with single-agent docetaxel (75–100 mg/m$^2$ every 21 days) for three cycles (the first cycle was at 75 mg/m$^2$ if tolerated docetaxel was to be escalated to 100 mg/m$^2$ for the second subsequent cycles). On both arms, treatment was limited to six total cycles of therapy (i.e., three of the platinum-based regimens and three of the taxane). Treatment at the time of relapse or progression after six cycles was at the discretion of the individual investigator. Cases with early evidence of progression before receiving all three cycles of the initial regimen (i.e., carboplatin/gemcitabine or cisplatin/vinorelbine) were to proceed immediately to therapy with the taxane. Standard SWOG response criteria were used (9), and toxicity was reported according to National Cancer Institute Common Toxicity Criteria, version 2.0. Treatment day dose modifications (i.e., days 1 or 8) for hematological toxicity were 25% reductions for either an absolute neutrophil count of $\leq 1,500$ but $\geq 1,000$ or a platelet count of 75,000–99,000/mm$^3$ with doses to be delayed for up to 2 weeks if ANC was $<1,000$ or platelet count $<75,000$/mm$^3$. Doses for all agents were reduced 25% in subsequent cycles for neutropenic fever. In arm 2, cisplatin was held if either serum creatinine was $>2.0$ mg/dl or calculated creatinine clearance was $<50$ ml/min. For nonhematological toxicities doses were either deleted for grade 2–3 toxicities or decreased by 50% (depending upon the nature of the toxicity). For grade 4 toxicity, doses were to be held until resolution of the toxicity to less than or equal to grade 1.

Study Design and Treatment Evaluations. The main objective of this study was to test whether either of these two regimens had promise in terms of increasing survival. Survival was calculated from the date of enrollment until the date of death or last contact using the Kaplan-Meier method (10). Each arm was to be analyzed separately. One or both of the regimens would be considered promising if the true median survival were 12 months or greater and of no additional interest if the true median survival were $\leq$8 months. The study was designed to accrue 80 patients to each arm over a period of 8 months followed by an additional year of follow-up to confer power of 0.90 for a one-sided 0.05 level test of 8 versus 12 months median survival. Actual accrual was 95 eligible and assessable patients on arm 1 and 83 eligible, analyzable patients on arm 2 over an 11-month accrual period. With the current 30 months of additional follow-up, the actual power is $\sim 98\%$ for each arm. The study was not powered to allow for comparison of the arms in terms of the end points of survival and response; however, the rates of selected toxicities were compared across the arms in an exploratory fashion using a $\chi^2$ test.

In addition, a secondary objective was assessment of incremental response to each part of the protocol treatment (initial therapy, sequential therapy). Tumor assessments were to be performed after three and six cycles of therapy. Patients who had progressive disease or stable disease during initial therapy and then experienced a response were regarded as improved; patients who had a partial response, which became a complete response, were also regarded as improved. A patient who had any response or stable disease and maintained that status was regarded as stable. Any patient with a response or stable disease or who had progressive disease initially and progressed with sequential therapy was regarded as exhibiting a worsening condition.

RESULTS

Demographics. A total of 204 patients were accrued, of whom, 178 are eligible and evaluable. Twenty-four patients were ineligible, 11 on Arm 1 and 13 on Arm 2. Two patients on arms 1 and 5 on arm 2 were ineligible due to staging error. The remaining patients were deemed ineligible based on lack of required baseline data or incorrect histology (one case). Two additional patients (both on arm 2) never received protocol therapy and are not included in the analyses. Accrual exceeded the statistically required 160 patients due to SWOG policy that study opening or closure only occurs at regular monthly intervals.

Table 1 summarizes the patient population. Consistent with prior SWOG studies, 80% of patients on arm 1 and 85% of patients on arm 2 had stage IV disease with the remainder stage IIIb on the basis of malignant pleural effusion. There were more female than male patients on arm 2, which approached statistical significance ($P = 0.054$).

Response and Survival. Response rates are summarized in Table 2. Thirty-seven patients had inadequate data for response assessment. This was due to failure to reassess all known
Sequential Chemotherapy in NSCLC (SWOG 9806)

The median overall survival for both arms was 9 months (arm 1, 95% confidence interval [CI] 7.2–10.0; arm 2, 95% CI 6.9–9.7). The median progression-free survivals were also the same for both arms at 4 months (arm 1, 95% CI 3.5–5.3; arm 2, 95% CI 4.0–5.5). One-year and 2-year survivals were 34% (95% CI 24–34) and 13% (95% CI 6–20%) on arm 1 and 36% (95% CI 26–46) and 8% (95% CI 2–14) on Arm 2. One- and 2-year progression-free survival for arm 1 was 25% and for arm 2, 22%, respectively, and 14% (95% CI 6–22) and 3% (95% CI 0–5) for arm 2, respectively.

**Salvage Therapy.** The protocol did not mandate that therapy subsequent to withdrawal from the protocol be recorded. Review of the study records demonstrates that a substantial fraction of the patients received either additional treatment with the original study medications or therapy with other drugs. On arm 1, 40 patients (42%) received additional treatment. Twelve received additional carboplatin/gemcitabine, 3 paclitaxel, 8 docetaxel, 9 vinorelbine or carboplatin/vinorelbine, and 8 received other agents (including experimental drugs). On arm 2, 25 patients (30%) received additional therapy. Six received additional cisplatin/vinorelbine, 11 gemcitabine or carboplatin/gemcitabine, 3 paclitaxel or carboplatin/paclitaxel, and 5 received other drugs. On both arms, some patients received more than one additional line of therapy.

**Toxicity.** The majority of patients (55% on arm 1 and 52% on arm 2) received all six cycles of therapy. Approximately 75% of patients on both arms received at least one cycle of taxane therapy. There were, however, differences in the toxicity profile of the two regimens, with patients on arm 1 experiencing more platelet toxicity and patients on arm 2 experiencing more nausea, neurological toxicity, and thrombotic events (Tables 4 and 5). There were eight fatal toxicities: arm 1, infection with neutropenia (2); congestive heart failure (1); arm 2, infection with neutropenia (2); respiratory infection without neutropenia (1); adult respiratory distress syndrome (1); and pulmonary fibrosis (1).

**DISCUSSION**

This study, representing the first cooperative group trial of planned sequential chemotherapy in NSCLC, demonstrates the feasibility of this treatment strategy. There is strong theoretical and biological rationale for this approach. Mathematical modeling by Day (11) as well as Norton and Simon (12) indicates that sequential treatment may be superior to concurrent therapy. The Day model predicts that the most active drug/regimen should be used as a consolidation treatment to optimize results. Recent laboratory (13) and clinical data (14) demonstrate that taxanes have activity in platinum-resistant NSCLC and improve survival compared with supportive care when given as second-
line therapy (15). In preclinical models and clinical experience, taxanes do not require the presence of an intact p53 pathway for apoptosis induction in contrast to DNA-damaging agents, including cisplatin (16, 17). As loss of functional p53 commonly occurs in lung cancer, sequential use of a taxane after a platinum (or other p53-dependent drug/regimen) and before the emergence of clinical drug resistance is theoretically attractive.

Another rationale for exploring sequential therapy is optimizing dose delivery. In particular, three drug regimens for NSCLC always compromise drug doses to avoid excessive myelosuppression. There is mounting evidence that paclitaxel demonstrates a complex threshold effect for antitumor activity in NSCLC dependent upon dose and infusion duration. Although initial studies delivered paclitaxel over 24 h, more recent studies have decreased infusion time to 3 h or to even 1 h. Of note, studies using paclitaxel/platinum combinations in which paclitaxel is administered at 175 mg/m² over 3 h failed to achieve improved survival compared with older platinum-based combinations or even cisplatin alone (18). In contrast, the Eastern Cooperative Oncology Group trial that administered paclitaxel over 24 h at 135 or 250 mg/m² demonstrated superior survival (1). In addition, Kosmidis demonstrated a higher response rate, longer time-to-progression, and a trend toward better overall survival in a randomized Phase II trial using 3-h administration of paclitaxel (225 versus 175 mg/m²), each in combination with carboplatin at area under the curve = 6 mg/ml × min (19). These considerations regarding paclitaxel dose and schedule may be important in interpreting the results of three drug regimens in which paclitaxel is administered at 175 mg/m² over 3 h or 200 mg/m² over 1 h (20, 21).

Additional support for the concept of sequential therapy comes from two recent articles documenting the lack of efficacy of more than three to four cycles of a specific platinum-based chemotherapy regimen. Smith compared three and six cycles of mitomycin, vindesine, and cisplatin in patients with advanced NSCLC and found no difference in terms of response or survival (22). Similarly, Socinski et al. (23) evaluated treatment with four cycles of carboplatin and paclitaxel versus an unlimited number (depending upon patient and physician tolerance) and also found no difference in terms of response or survival. Both studies demonstrated increased toxicity with continued treatment. Given the lack of evidence for continuation of a single regimen beyond three to four cycles in the palliative treatment of metastatic NSCLC and the unquestionable presence of residual disease, planned sequential administration of additional agents with different mechanisms of action is a reasonable strategy to explore. Furthermore, such a change in therapy reduces the potential for cumulative toxic effects.

The use of a taxane after other agents in lung cancer rather than the reverse order is supported (although not proven) by the randomized Phase II study performed by Manegold et al. (24), which demonstrated that gemcitabine followed by docetaxel was more effective than the reverse order. In this study, patients received either single-agent gemcitabine or docetaxel until progression and then the other agent. Median survival was 9 months for gemcitabine followed by docetaxel as opposed to 5.5 months for the reverse order.

In addition, the recent experience of SWOG in pathologically documented stage IIIB disease in which chemoradiotherapy with cisplatin/etoposide and concurrent radiotherapy was followed by docetaxel. This study has demonstrated encouraging survival in the cooperative group setting with 37% of patients alive at 3 years (25).

Unfortunately, although the current study demonstrated the feasibility of both regimens and median survivals were modestly longer than those achieved in prior chemotherapy trials by SWOG in this patient population, in neither arm did the results meet the statistical criteria warranting further study. There are several possible reasons. First, the agents used sequentially may not be truly non-cross-resistant. In addition, the large burden of disease in patients with stage IV NSCLC increases the possibility that clones resistant to all of the agents selected may have already evolved. Lastly, although both docetaxel and paclitaxel are active agents in second-line management of NSCLC, each has only a modest degree of effect.

Although disappointing, these results do not disprove the underlying rationale for a sequential approach to chemotherapy in advanced NSCLC. The availability of new agents, some of which appear to demonstrate activity in pretreated patients and that have unique mechanisms of action, argues for continued evaluation of this strategy.

### Table 4: Hematologic toxicity more than or equal to grade 3 (percentage of patients)

<table>
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<th>Arm 1 (n = 95)</th>
<th>Arm 2 (n = 83)</th>
<th>P</th>
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<tr>
<td>Toxicity/Grade</td>
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<td></td>
<td></td>
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<tr>
<td>Anemia</td>
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<td>18</td>
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<td>Thrombocytopenia</td>
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<td>Neutropenia</td>
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<td>Fever + neutropenia</td>
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<td>Packed RBC transfusions</td>
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<td>0.03</td>
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<tr>
<td>Platelet transfusions</td>
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<td>Hemorrhage</td>
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Abbreviations: ns, not significant.

### Table 5: Nonhematologic toxicity more than grade 3 (percentage of patients)

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<th>Arm 1 (n = 95)</th>
<th>Arm 2 (n = 83)</th>
<th>P</th>
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<tr>
<td>Toxicity/Grade</td>
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<tr>
<td>Anorexia</td>
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<tr>
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<td>Dyspnea</td>
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<tr>
<td>Fatigue/Malaise/Lethargy</td>
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<td>0</td>
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<tr>
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<tr>
<td>Neuropathy (sensory)</td>
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<td>1</td>
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<tr>
<td>Pulmonary fibrosis</td>
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<tr>
<td>Vomiting</td>
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<td>10</td>
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<td>Thrombosis/Embolism</td>
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Abbreviations: ns, not significant.
REFERENCES
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