Treatment of Patients with Advanced Nonsmall Cell Lung Carcinoma Using Docetaxel and Gemcitabine plus Granulocyte-Colony Stimulating Factor

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BACKGROUND. A combination regimen comprised of docetaxel, gemcitabine, and granulocyte-colony stimulating factor (G-CSF) was studied in patients with advanced nonsmall cell lung carcinoma (NSCLC) to determine its antitumor efficacy and tolerance.

METHODS. Thirty-four patients with advanced measurable NSCLC (3 patients with Stage IIIB and 31 patients with Stage IV disease) were treated with an intravenous combination chemotherapy regimen comprised of docetaxel, 80 mg/m^2, on Day 1 and gemcitabine, 1000 mg/m^2, on Days 1 and 10; G-CSF, 5 μg/kg, was administered subcutaneously between Days 2 and 8. Treatment cycles were repeated every 3 weeks. All patients were evaluable for toxicity and response assessment. A total of 163 courses was administered.

RESULTS. Objective tumor response was noted in 17 patients (50%; 95% confidence interval, 32.5–67.5%), including 2 complete responses (6%) and 15 partial responses (44%). There was no change in 10 patients (29%) and 7 patients developed progressive disease. The median duration of response was 6.5 months (range, 3–15 months) and the median time to disease progression for all patients was 6.8 months (range, 1.8–18 months). The median overall survival time was 13.0 months (range, 2.5–23+ months) with a 1-year survival rate of 55.8%. Myelosuppression was the most frequently encountered adverse reaction, although World Health Organization Grade 3 or 4 leukocytopenia and/or granulocytopenia occurred in only 18% and 24% of patients, respectively. Other toxicities generally were mild to moderate, and always fully reversible.

CONCLUSIONS. With a response rate of 50% and a median survival time of 13 months, the drug combination described in the current study appears to have significant activity against advanced metastatic NSCLC. Due to its fairly good tolerance and ease of administration, further investigation of this regimen appears warranted. ***Cancer* 2000;89:516–22.** *© 2000 American Cancer Society.*

KEYWORDS: advanced nonsmall cell lung carcinoma (NSCLC), docetaxel, gemcitabine, granulocyte-colony stimulating factor (G-CSF).

According to current statistics, lung cancer continues to be the leading cause of cancer death for both males and females.[1] Nonsmall cell lung carcinoma (NSCLC) represents 70–80% of newly diagnosed lung carcinomas, and more than half of these patients are inoperable at the time of initial diagnosis because of locally advanced (Stage IIIB) or metastatic disease (Stage IV). Currently, the disease at either stage is uniformly fatal with a median survival expectancy of only a few months.[2,3]

The treatment of patients with advanced NSCLC has proven to be difficult, and until recently, the use of chemotherapy was considered

to be of doubtful value. Meta-analyses of randomized clinical studies comparing combination chemotherapy versus "best supportive care," however, have disclosed a statistically significant survival advantage for patients who receive chemotherapy.[4–8] Because the net benefit of conventional cytotoxic treatment, in fact, seems very small (approximately a 1.5-month increase in median survival), it is obvious that further clinical research efforts are required; they should be directed toward defining new more effective drugs and combination regimens, resulting in palliation of symptoms with as few side effects as possible.

In recent years, a relatively large number of new active agents have become available for the treatment of NSCLC; among these agents, docetaxel and gemcitabine are certainly some of the most noteworthy. Both of these new agents have proven activity as first-line single agents: with docetaxel, a semisynthetic taxoid, response rates of 21% to 33% and a median survival time of 9.2 months have been reported;[9–12] with gemcitabine, a nucleoside antimetabolite of deoxycytidine, response rates of 20–22.5% and a median survival of 6–8 months can be expected.[13–16] The two agents have different mechanisms of action, opening up the possibility of additive if not synergistic effects. Gemcitabine, by its unique property of being incorporated on the end of an elongating DNA strand, the addition of a deoxynucleotide (leading to the so-called "masked-chain termination"), and the inhibition of ribonucleotide reductase, leads to inhibition of DNA synthesis.[17] Docetaxel, conversely, induces important disturbances of G_2- to M-phase (mainly in the S-phase) that could lead to cell death.[18]

Several dose-finding studies of the combination of docetaxel and gemcitabine have been performed or have been presented in their preliminary form. Spiridonidis et al.[19] treated 40 patients with solid tumors with the combination gemcitabine 800 mg/m^2 given on Days 1, 8, and 15 every 4 weeks and docetaxel given either on Day 1 or on Day 15 at doses escalating from 45 to 100 mg/m^2. Major toxicities were neutropenia, liver function disturbances, and skin toxicity. A dose of 800 mg/m^2 gemcitabine in combination with 100 mg/m^2 docetaxel was considered feasible. Nine of 21 patients (43%) with advanced NSCLC responded to the treatment. In another Phase I dose-finding study, docetaxel was given on Day 1 and gemcitabine on Days 1, 8, and 15 of a 4-week cycle.[20] Preliminary results showed the feasibility of doses of 800 and 80 mg/m^2 for gemcitabine and docetaxel, respectively. Also in this study, responses were observed. A principal reason for administering gemcitabine on Days 1 and 10 rather than on Days 1, 8, and 15 is to counteract the likelihood of myelosuppression (on Day 8) and the resultant need for dose reductions and/or treatment delays due to coadministration of docetaxel on Day 1.[21]

It currently remains unclear what constitutes the optimal regimen to be used as standard therapy for patients with advanced NSCLC. Furthermore, there is a clear need for an alternative to existing cisplatin-based chemotherapy for NSCLC and for regimens that improve on its efficacy. In view of the mentioned single-agent activity in NSCLC and the lack of overlapping toxicity of docetaxel and gemcitabine, their different mechanisms of action, as well as preliminary encouraging data that were noted in dose-finding studies, including our own pilot Phase I series (unpublished data), the current study was initiated. The objective was to perform a more comprehensive Phase II evaluation of the activity and tolerance of this particular drug combination in patients with advanced, i.e., Stage IIIB and IV NSCLC. To prevent and counteract myelosuppression that was assumed to represent the dose-limiting toxicity, we routinely used prophylactic administration of the hematopoetic growth factor granulocyte-colony stimulating factor (G-CSF).

PATIENTS AND METHODS

Patient Selection

Between June 1997 and December 1998, 34 patients with inoperable, locally advanced or metastatic NSCLC were entered in this trial. Eligible patients had histologically or cytologically confirmed Stage IIIB or IV disease[22] with ≥ 1 bidimensionally measurable lesion and may not have received previous chemotherapy. Patients who had undergone prior radiotherapy were acceptable, if there was measurable disease outside of the radiation port, at least 3 weeks had elapsed since they completed therapy, and all acute toxic effects of treatment had resolved. Patients were required to be age ≤ 75 years, to have an anticipated life expectancy of 3 months, to have a World Health Organization (WHO) performance status of ≤ 2, and to have adequate renal (serum creatinine level < 1.5 mg/dL), hepatic (total serum bilirubin, < 1.5 mg/dL; and serum transaminase levels of < 2 times the upper limits of normal), and bone marrow functions (leukocyte count, $> 4000/\mu$L; platelet count, $>100{,}000/\mu$L). Patients with severe concurrent medical conditions, central nervous system metastases, or a history of prior malignancy were not eligible for treatment. All patients gave informed consent according to institutional guidelines before study entry.

Treatment Plan

Chemotherapy consisted of docetaxel 80 mg/m^2 given by intravenous (i.v.) infusion over 90 minutes on Day

1 and gemcitabine 1000 mg/m^2 administered over 30 minutes on Days 1 and 10; recombinant human G-CSF 5 μg/kg was given prophylactically by subcutaneous injection from Days 2–8. Treatment cycles were repeated every 3 weeks. Patients continued to receive their assigned treatment for a total of six courses, provided they had sufficiently recovered from drug-related side effects and did not develop progressive disease. In addition to a standard oral steroids premedication (dexametasone, 8 mg orally 12 and 4 hours before docetaxel infusion and 8 mg twice daily for 3 additional days), antiemetic treatment with intravenous ondansetron and dexamethasone was given routinely before the administration of chemotherapy.

Dose adjustments were based on hematologic nadir values and occurrence/degree of other systemic side effects during the previous cycle. Patients who experienced WHO Grade 4 hematologic side effects or chemotherapy-induced febrile neutropenia requiring parenteral antibiotics were treated at 25% reduced drug doses. Nonhematologic side effects of WHO Grade 3 or higher (except alopecia) also mandated a 25% dosage reduction of both chemotherapeutic drugs. Recovery from all hematologic and/or other organic side effects up to and including Grade 1 was required before treatment was resumed. In instances of a delay longer than 2 weeks, chemotherapy was withdrawn because of prolonged toxicity.

Pretreatment and Follow-Up Evaluation

Within 2 weeks before initiating therapy, each patient was assessed by physical examination, complete medical history, chest X-ray, computed tomography (CT) of the chest and abdomen, radionuclide bone scan with X-ray details of hot spots, electrocardiogram, and routine laboratory studies. The latter consisted of a complete blood cell count, including differential leukocyte, electrolytes, calcium, creatinine, blood urea nitrogen, total bilirubin, alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase levels, total protein and albumin, prothrombin, and partial thromboplastin time. During treatment, patient monitoring included a weekly blood count and a biochemical profile before each cycle.

Follow-up history, physical examination, and toxicity assessment were performed before each 3-week course of therapy; when needed to determine response, pertinent CT scans were repeated every 2 months. Designations of complete response, partial response, no change, and progressive disease were based on the standardized response definitions established by the WHO. Similarly, toxicity evaluations were based on the World Health Organization's common toxicity criteria.

STATISTICAL METHODS

Using standard statistical methods, a two-stage design was used in the protocol.[23] If no complete response (CR) or partial response (PR) was noted for the first 14 patients, a response rate of $>$ 20% could be excluded with 95% confidence and accrual was stopped. If at least 1 CR or PR was observed, $\geq$ 30 patients were to be entered in the study to determine the response rate more accurately. All patients who received at least two cycles were assessable for response, and all patients who received at least one cycle were assessable for toxicity. The duration of response was calculated as the time from first documentation of objective major (i.e., complete or partial) response to first documentation of disease progression. The time to progression was calculated from study entry until the day of the first evidence of tumor progression. The actuarial survival was estimated by the methods of Kaplan and Meier,[24] and 95% confidence intervals for response rate were calculated using methods for exact binominal confidence intervals.[25] Qualitative factors were compared by Pearsons χ^2 contingency table analysis.

RESULTS

Patient Characteristics

Between June 1997 and December 1998, a total of 34 patients was included in this study. Their pretreatment characteristics are shown in Table 1. Nine patients were female and 25 were male. Their median age was 61 years with 16 patients (47%) age $>$ 65 years. The median WHO performance status was 1. The most common histologic subtype was adenocarcinoma, comprising approximately 50% of our patients. Three patients had Stage IIIB disease, and 31 patients had Stage IV disease. Eight patients had undergone prior surgery, including 5 with a curative-intent surgery and recurrence free intervals of 8, 9, 14, 15, and 16 months, respectively; 1 had a palliative left segment resection, 1 had undergone palliative orthopedic surgery, and 1 had undergone a vena cava stent implantation. Apart from one patient who subsequently received consolidating radiotherapy, eight more patients received palliative radiation because of skeletal pain due to osteolytic lesions before initiating chemotherapy.

A total of 163 treatment cycles was administrated to our patients (median, 5; range, 2–6). All patients completed two cycles of therapy and were assessable for response. One patient discontinued treatment after the second cycle before response could formally be assessed. To report results by "intent-to treatment," we included this patient in the analysis as a nonresponder.

TABLE 1
Patient Characteristics

Characteristic	No. (%)
No. of patients entered	34
Age (yrs)	
Median	61
Range	41–75
Gender	
Female	9 (26.5)
Male	25 (73.5)
Performance status	
WHO 0	10 (29.5)
WHO 1	16 (47)
WHO 2	8 (23.5)
Histologic subtype	
Adenocarcinoma	18 (53)
Squamous cell carcinoma	14 (41)
Large cell carcinoma	1 (3)
Unclassified NSCLC	1 (3)
Stage	
IIIB	3 (9)
IV	31 (91)
No. of disease sites	
1	2 (6)
2	11 (32)
≥ 3	21 (62)
Previous therapy	
Surgery	8 (23.5)
Radiotherapy	9 (26.5)

WHO: World Health Organization; NSCLC: nonsmall cell lung carcinoma.

TABLE 2
No. of Patients with Treatment-Associated Side Effects (Worst Ever)

	WHO grade			
Side effect	1	2	3	4
Hematologic toxicity				
Leukocytopenia	9 (26.5)	7 (20.5)	4 (12)	2 (6)
Granulocytopenia	4 (12)	12 (35)	5 (15)	3 (9)
Thrombocytopenia	11 (32)	8 (23.5)	1 (3)	—
Anemia	8 (23.5)	4 (12)	—	—
Nonhematologic toxicity				
Stomatitis	4 (12)	4 (12)	—	—
Nausea/emesis	7 (20.5)	4 (12)	3 (9)	—
Alopecia	4 (12)	12 (35)	12 (35)	—
Infection	3 (9)	3 (9)	2 (6)	—
Constipation	1 (3)	2 (6)	—	—
Peripheral neuropathy	6 (18)	3 (9)	1 (3)	—
Diarrhea	4 (12)	3 (9)	—	—
Phlebitis	2 (6)	—	—	—
Fatigue	10 (29.5)	2 (6)	—	—
G-CSF-related fever/myalgias	1 (3)	2 (6)	—	—

WHO: World Health Organization; G-CSF: granulocyte-colony stimulating factor.

Response to Treatment

Two of 34 patients (6%) had a CR with a duration of 3 months and 10 months, respectively, and 15 patients (44%) had a PR with a median duration of 6.5 months (range, 3–15 months), yielding an overall response rate of 50% (95% confidence interval, 32.5–67.5%). The median time to objective tumor response was 2.7 months (range, 1.8–3.5 months). Objective responses occurred with equal frequency in all histologic subtypes and in patients with Stage IIIB (2 of 3) and IV (15 of 31) disease, although only in 1 of 8 patients (12.5%) presented with a WHO performance status of 2. Ten additional patients (29%) had stable disease for a median duration of 6 months (range, 4–12 months), and 7 progressed during chemotherapy. The median time to progression for all patients was 6.8 months (range, 1.8–18 months). The median overall survival was 13 months (range, 2.5–23+ months; 95% CI, 10.8–15.2 months), and the actuarial 1-year survival was 55.8% (95% CI, 0.38–0.73%) with a median follow-up duration of the 15 surviving patients of 15.0 months (Table 1).

Toxicity

The most common treatment-associated toxic effect was myelosuppression. Leukopenia and granulocytopenia occurred in 22 (64.7%) and 24 (70.6%) patients, respectively, but was Grade 3 or 4 in only 6 (18%) and 8 (24%) patients, respectively. The median nadir leukocyte count was 4.100/μL (range, 600–15.300/μL), and the median leukocyte count recovery to 3.000/μL was short (i.e., 96% of episodes of leukopenia resolved within 7 days). The variations in granulocyte counts paralleled those of leukocytes, and the median nadir count was 1.980/μL (range, 150–8.510/μL). Thrombocytopenia was noted in a total of 20 patients but was rated severe (Grade 3) in only 1 patient (3%); similarly, there were no bleeding episodes. Eight patients developed documented infection, although there were only two episodes of febrile neutropenia that required hospitalization. Both patients were treated successfully with broad-spectrum antibiotics. Nonhematologic side effects generally were mild to moderate, always fully reversible, and easy to treat. Severe adverse reactions included Grade 3 emesis and peripheral neuropathy in 3 patients each. Total alopecia was noted in 12 cases (35%) and was minor or minimal in 47%.

Treatment was discontinued due to drug-related toxicity in two patients (including one patient each with docetaxel-induced hypersensitivity and progressive peripheral neuropathy) and for other reasons in three patients (pulmonary embolism, abdominal surgery, and personal reasons, respectively). Seven patients (21%) had at least 1 treatment delay of 1 week at some time during therapy, and the total number of delayed courses was 14 (9%). The reasons for treatment delay were patient's request unrelated to the

disease or treatment (five cycles), granulocytopenia (four cycles), thrombocytopenia (three cycles), and intercurrent respiratory infection (two cycles). Only 3 patients had a 25% dose reduction of cytotoxic drugs during treatment according to the study protocol, because of Grade 4 granulocytopenia (n = 1) with or without infection (n = 2).

Dose intensity was calculated for each patient and for each drug. The mean given dose intensity was 88.6% of the projected dose for both docetaxel and gemcitabine. The administered mean dose of docetaxel was 23.6 mg/m^2/week (range, 8.9–26.7 mg/m) and the mean dose of gemcitabine was 591 mg/m^2/week (range, 222–667 mg/m).

DISCUSSION

During the past few years, a number of new chemotherapeutic agents have been shown to be active against NSCLC, including docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan. Several different combination regimens with these new drugs currently are undergoing clinical investigation in an attempt to further improve an therapeutic armamentarium against this common malignancy that continues to replace the leading cause of death in both men and woman.[26,27]

In the current trial, we have investigated the activity, tolerance, and safety of such a novel noncisplatin containing first-line combination regimen consisting of docetaxel and gemcitabine in patients with advanced NSCLC. The rationale for combining these two drugs included their distinct mechanisms of action with different intracellular targets, high levels of single-agent activity in this disease, and recently published Phase I/II data in various tumor types, suggesting potential drug synergism between the taxanes and gemcitabine.[19–21,27–30] To allow administration of sufficient cytotoxic drug doses, and to prevent/counteract neutropenia that was assumed to represent the dose-limiting toxicity, a rather cost-effective short term course of G-CSF routinely was given to our patients.[31]

Because it concerns the therapeutic potential of this two-drug combination regimen, we noted an encouraging objective response rate of 50% in our intent-to-treat patients, including 2 CRs (6%) and 15 PRs lasting for a median duration of 6.5 months. The survival data observed in the current study (median, 13 months; 1-year survival, 55.8%) are particularly encouraging, taking into account the poor prognostic factors of our patients. Indeed, 91% had Stage IV disease, 71% had a WHO performance status of 1 or 2, and 62% had more than 2 organs involved. Therapeutic results seem at least comparable to those achieved with other cisplatin- or carboplatin-based regimens, which have resulted in median survival times ranging from 5.5 to 12 months.[32–35] Of note, the observed survival data are almost superimposable with the outcome of another recently published patient series treated with the same drug combination, although Georgoulias et al.[21] have used a higher docetaxel dose, and their patient population tended to have more favorable pretreatment characteristics. In this Phase II study, 51 NSCLC patients were treated with 3 weekly courses of gemcitabine 900 mg/m^2 administered on Days 1 and 8, docetaxel 100 mg/m^2 administered on Day 8, and G-CSF 150 mcg/m^2 on Days 9–15. Seventy-one percent (vs. 91% in the current series) had Stage IV disease, 59% (vs. 71%) had a WHO performance status of 1 or 2, and 20% (vs. 62%) had more than 2 involved organs. PRs were reported in 19 patients (37.5%) and lasted for a median duration of 6 months. The median survival was 13 months, and the actuarial 1-year survival was 50.7%.

A noteworthy observation in the current study (and as also documented by Georgoulias et al.[21]) represents the finding that the encouraging therapeutic results were obtained with minimal toxicity. Grade 3 or 4 neutropenia occurred in only 24% of our patients and rarely was associated with infectious complications. The prophylactic use of G-CSF could be a possible explanation for the low incidence rate of severe neutropenia, although other mechanisms, such as a bone marrow-sparing effect of the combination cannot be ruled out.[21] According to this possibility and the observed hematologic toxicity profile of the investigated docetaxel and gemcitabine regimen, one might consider its use without G-CSF, and reverse hematopoetic growth factor support for patients with unpredictable neutropenia. Nonhematologic toxicity also was mild; apart from alopecia, the most common adverse events observed with the combination as used in the current study were nausea/emesis (41%), fatigue (35%), and peripheral neuropathy (29%). These symptoms, however, rarely exceeded WHO Grade 1 or 2, and only 2 patients discontinued treatment because of drug-related toxicity. It seems noteworthy that patients with performance status 2 did not appear to suffer more toxicity than patients with performance status 0–1, as noted in a recently published trial of the Eastern Cooperative Group trial comparing paclitaxel plus cisplatin versus cisplatin plus etoposide.[36] This observation might be related to the use of different chemotherapeutic drug regimens with different toxicity profiles or simply to the small number of patients treated in the current Phase II investigation.

With a 50% major response rate and disease stabilization in approximately an additional 33% of our

patients, this combination regimen of docetaxel and gemcitabine seems to have major activity against advanced NSCLC. Due to its tolerance and ease of administration on an outpatient basis, further investigation of this combination in the palliative-intent care setting, such as a comparative trial with cisplatin- or carboplatin-based regimens, appears to be of considerable interest. A randomized Phase II trial investigating docetaxel plus cisplatin versus a more dose-intensive docetaxel plus gemcitabine regimen is currently ongoing;[37] preliminary results suggested an overall comparable activity and toxicity profile, although the latter combination, in fact, may have certain advantages in terms of response activity in patients with adenocarcinomas and a somewhat lower incidence of specific adverse reactions such as neutropenia, neurotoxicity, and diarrhea.

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