Phase II Study of Pemetrexed-Gemcitabine Combination in Patients with Advanced-Stage Non-Small Cell Lung Cancer

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ABSTRACT

Purpose: Cisplatin is one of the most active agents for the treatment of non-small cell lung cancer (NSCLC). It is also known for significant toxicity, which makes it unsuitable for certain patients. Our purpose was to evaluate the efficacy and toxicity of a promising cisplatin-free combination, gemcitabine plus pemetrexed, in NSCLC.

Experimental Design: Chemo-naive patients with inoperable NSCLC were eligible for this study. Gemcitabine (1250 mg/m2) was given intravenously on days 1 and 8, followed by intravenous pemetrexed (500 mg/m2) on day 8. After inclusion of 13 patients, folic acid and vitamin B12 supplementation was added to lower pemetrexed-induced toxicity. Quality of life was assessed with the Lung Cancer Symptom Scale.

Results: Sixty patients enrolled; 58 were evaluable for response. All patients had a World Health Organization performance status of 0 or 1. Eighty-seven percent had stage IV disease. Nine patients had a confirmed partial response [overall response rate, 15.5%; 95% confidence interval (CI), 7.3–27.4%]. Twenty-nine (50.0%) patients had stable disease. Median overall survival was 10.1 months (95% CI, 7.3–27.4%). Median progression-free survival was 5.0 months (95% CI, 2.6–9.1). Median progression-free survival was 5.0 months. Median response duration was 3.3 months. There were no deaths attributed to treatment. Common Toxicity Criteria grade 3/4 toxicities were neutropenia (61.7%), febrile neutropenia (16.7%), fatigue (23.3%), and elevations of aspartate aminotransferase (15.0%) and alanine aminotransferase (20.0%).

Conclusions: This combination had good tolerance and achieved promising overall survival with extended 1- and 2-year survival rates. This cisplatin-free regimen warrants further evaluation in randomized trials.

INTRODUCTION

Pemetrexed (LY231514, Alimta; Eli Lilly and Company, Indianapolis, IN) is a novel antifolate that is metabolized intracellularly to a pentaglutamate form. Pemetrexed inhibits three enzymes (thymidylate synthase, dihydrofolate reductase, and glycaminide ribonucleotide transferase) involved in folate metabolism and DNA synthesis (1–3). The cytotoxicity of pemetrexed is caused by inhibition of both the pyrimidine and purine pathways. The maximum tolerated dose established in Phase I studies of pemetrexed was 600 mg/m2 every 3 weeks (4, 5). This dose was later reduced to 500 mg/m2 every 3 weeks in several Phase II trials, particularly when used in combination with other cytotoxic agents (6, 7). Folic acid and vitamin B12 supplementation became a requirement for pemetrexed-based therapy early in this study, when analysis of safety data from multiple pemetrexed trials suggested that supplementation may decrease toxicity (8). Single-agent pemetrexed was tested in two Phase II non-small cell lung cancer (NSCLC) trials enrolling 92 chemo-naive patients (without vitamin supplementation) by Clarke et al. (9) and Rusthoven et al. (7). Response rates of 15.8% and 23.3% and median survivals of 7.2 and 9.2 months were observed, respectively. In these two studies, the main toxicities reported were grade 3/4 neutropenia (42% and 39%) and grade 3/4 skin rash (31% and 39%).

Gemcitabine (Gemzar; Eli Lilly and Company) is a pyrimidine antimetabolite that is intracellularly transformed to difluoro deoxycytidine triphosphatase. Its incorporation into DNA results in chain termination. Gemcitabine also inhibits ribonucleotide reductase, an enzyme required for deoxyribonucleotide formation and DNA synthesis (10). Gemcitabine has been widely explored in NSCLC, as a single-agent and in combination. The United States Food and Drug Administration-approved dose is 1000 mg/m2 weekly for 3 weeks every 4 weeks (11, 12) or 1250 mg/m2 weekly for 2 weeks every 3 weeks (13). In a Phase II study of gemcitabine (1250 mg/m2) weekly for 3 of 4 weeks enrolling 161 patients with advanced NSCLC, the response rate was 21.8%, and median survival was 11.5 months (13). Main toxicities were grade 3 neutropenia, nausea, and elevations of hepatic transaminases.

Because pemetrexed and gemcitabine have both shown single-agent activity against a wide range of solid tumors including NSCLC (7, 9, 11, 12, 14, 15), the combination of these
An Outpatient Cisplatin-Free Regimen for Advanced NSCLC

Section of the document:

- **Patient Selection.** Eligible patients had histological or cytologic diagnosis of stage IIIB or IV NSCLC, with evidence of bidimensionally measurable disease. Any clinically significant effusion had to be drained and pleurodesis had to be performed at least 2 weeks before baseline imaging. Previous systemic chemotherapy, as well as prior radiation therapy to target lesions, was not permitted. Other eligibility criteria included the following: age ≥ 18 years; World Health Organization performance status of 0 or 1; calculated creatinine clearance ≥ 45 ml/min (based on modified Cockcroft and Gault method; Ref. 17); adequate hepatic function (i.e., serum bilirubin of ≤1.5 times the upper normal limit; alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase of ≤3.0 times the upper normal limit or ≤5.0 times the upper normal limit in case of liver metastases); adequate bone marrow function (absolute neutrophil count ≥ 1.5 × 10^9/liter, platelet count ≥ 150 × 10^9/liter, and hemoglobin ≥ 9 g/dl); albumin ≥ 3.0 g/dl; absence of >10% weight loss in the 6 weeks before inclusion; absence of serious concomitant illness that would compromise chemotherapy delivery; absence of second primary malignancy (except cervical carcinoma in situ and melanomatous skin cancer that was adequately treated); absence of clinical evidence of brain metastases; effective contraceptive methods in patients with reproductive potential and negative pregnancy test for women before study entry; and written informed consent.

- **Drug Administration.** Pemetrexed was supplied as a 40-mg/ml aqueous solution in vials of 200 or 1000 mg of the base compound. The appropriate dose of pemetrexed was added to 100 ml of normal saline for intravenous infusion. Gemcitabine was supplied as a lyophilized powder in 200- or 1000-mg vials. The appropriate dose was prepared with normal saline to make a solution containing approximately 10 mg/ml for intravenous infusion. Chemotherapy was given on a 3-week schedule and consisted of 1250 mg/m^2 gemcitabine over 30 min on days 1 and 8 and 500 mg/m^2 pemetrexed over 10 min on day 8, approximately 90 min after the gemcitabine infusion. Dose adjustments within a cycle were as follows: in case of Common Toxicity Criteria Version 2.0 (18) grade 3/4 neutropenia, thrombocytopenia, or nonhematological toxicity (except grade 3 transaminase elevation) after day 1, the day 8 doses were held until resolution of the toxicity, and pemetrexed and gemcitabine were given at full dose in case of a grade 3 toxicity and at 50% reduced dose in case of a grade 4 toxicity. No dose escalation was allowed after a dose reduction for the remainder of the study. The next cycle was not initiated until 14 days had elapsed from the administration of a delayed day 8 dose and until all toxicities resolved. Treatment could be delayed up to 35 days from the day 1 dose to allow a patient sufficient time to recover from all toxicities. If a further cycle could not be given by day 35, the patient was discontinued from study. For subsequent cycles, pemetrexed and gemcitabine doses were adjusted according to neutrophil and platelet nadir counts or maximum nonhematological toxicity from the preceding cycle. Treatment was interrupted for a persistent drop of creatinine clearance under 45 ml/min or the appearance of a clinically significant effusion. Beginning on December 10, 1999, folic acid (350–1000 µg/day orally) and vitamin B₁₂ (1000 µg) i.m. every 9 weeks became mandatory, starting 1 to 2 weeks before initiation of chemotherapy. Dexamethasone (4 mg or equivalent) was given orally twice daily the day before, the day of, and the day after pemetrexed infusion to prevent rash. Antiemetic treatment with a 5HT₃ antagonist and dexamethasone was recommended before each chemotherapy infusion. Dexamethasone was recommended for up to 2 days after the infusion. Salicylates or other nonsteroidal anti-inflammatory agents were interrupted 2 days before (5 days for long-acting agents), the day of, and 2 days after pemetrexed infusion to avoid any interaction with renal function.

**Measurement of Study End Points.** This multicenter study had response rate as the primary end point, and the Simon optimum sequential two-stage design was used (19). In stage 1, at least 7 of 30 enrolled patients had to have an objective tumor response to proceed to stage 2, where 30 additional patients were to be treated, for a total of 60 patients.

All patients who received one dose of chemotherapy were assessable for toxicity. A clinical and laboratory assessment was performed weekly, and toxicities were graded according to Common Toxicity Criteria. Within 3 weeks before the first cycle, tumor measurements were performed by computed tomography scan or magnetic resonance imaging. The same method of measurement was performed before every other cycle of therapy. Confirmation of response was performed 3–4 weeks after the first evidence of response. Patients were evaluable for response if they had a baseline exam and at least one follow-up exam and had received at least one cycle of chemotherapy. All sites with measurable lesions were followed for response. Measurements of unidimensional (i.e., single largest dimension) and...
bidimensional lesions (i.e., the product of the largest diameter and its largest perpendicular) were summed at each assessment, and the best response on study was recorded. A complete response required the disappearance of all clinical and radiological evidence of tumor for at least 3–4 weeks. A partial response required a ≥50% decrease in the sum of the products of the diameters of all measurable lesions for at least 3–4 weeks. Appearance of any new lesion or a ≥25% increase in the sum of the products of the diameters of measurable lesions compared with the smallest sum constituted progressive disease. Stable disease was a tumor decrease less than a partial response and a tumor increase less than progressive disease. Overall survival was defined as the time from study entry to the date of death or last follow-up. Progression-free survival was defined as the time from study entry until the date of disease progression or death from any cause or the date of last follow-up. Response duration was defined as the time of a complete response or partial response until disease progression. All survival estimates were calculated by the Kaplan-Meier method (20).

Before each cycle, symptoms and quality of life data were collected with the Lung Cancer Symptom Scale (LCSS), as reported by patients and investigators (21). The patient LCSS items are assessed as 100-mm visual analog scales, and scores were reported as 0 to 100, with 0 representing the best score. Clinically meaningful changes were defined as ≥10-mm changes from baseline that were maintained for at least two cycles. Patients were considered symptomatic if the baseline assessment was ≥10 mm. Observer LCSS scores were reported on 5-point categorical scales, and clinically meaningful changes were defined as ≥1-point changes from baseline that were maintained for at least two cycles. Patients with baseline assessment and at least one on-study assessment were evaluable for each of the LCSS analyses. Symptoms were classified as improved, worsened, or stable, based on the pattern of change; symptoms for patients without a confirmatory assessment were classified as unknown.

RESULTS

Patients. From August 1999 to May 2001, 72 patients were considered for inclusion and signed informed consent. After fulfillment of all baseline exams, 11 patients did not meet the inclusion criteria (7 had inadequate organ function, 1 did not have histological/cytologic confirmation, 1 had inadequate performance status, 1 had excess weight loss, and 1 had both inadequate organ function and performance status), and 1 patient withdrew consent. The demographic and disease characteristics of the 60 eligible patients are listed in Table 1. Among the 60 eligible patients, 47 received vitamin supplementation throughout their course of therapy, 10 received supplementation during part of their therapy, and 3 completed the study before vitamin supplementation was initiated.

Drug Administration. A total of 229 cycles were administered (median, 4; range, 1–12). Thirty-two patients (53.3%) received full doses of chemotherapy, 23 patients (38.3%) had dose reductions, and 5 patients (8.3%) had one omitted dose. Dose reduction was required in a total of 40 cycles (17.5%), 20 (50.0%) occurring at cycle 2, 6 occurring at cycle 3, 7 occurring at cycle 4, 3 occurring at cycle 5, and 1 each occurring at cycles 6, 9, 11, and 12. Reasons for dose reduction included neutropenia (82.5%), febrile neutropenia (7.5%), leukopenia (5.0%), and fatigue (5.0%). A dose delay was required in 28 patients (46.7%) and in 45 cycles (19.7%). For pemetrexed, the theoretical dose intensity was 166.7 mg/m2/week, and the actual mean dose intensity received was 145.4 mg/m2/week, representing a relative dose intensity of 87.2%. For gemcitabine, the theoretical dose intensity was 833.3 mg/m2/week, and the actual mean dose intensity received was 644.0 mg/m2/week, representing a relative dose intensity of 77.3%.

Antitumor Activity. Fifty-eight patients were evaluable for tumor response (seven had baseline computed tomography scans performed within 28 days of initiation of chemotherapy, instead of 21 days as defined by the protocol). Two of the enrolled patients were not evaluable: one patient had a baseline computed tomography scan done 42 days before treatment; and the other had no baseline computed tomography scan available. No patient had a complete response, but 9 patients (7 of them from the 30 patients in stage I of the trial) had a confirmed partial response, for an overall response rate of 15.5% [95% confidence interval (CI), 7.3–27.5%]. Twenty-nine patients (50.0%) had stable disease, 12 patients (20.7%) had progressive disease, and 8 patients (13.8%) were not evaluated (6 patients went off study before tumor evaluation, and 2 patients did not have a subsequent measure of same lesions recorded at baseline). Therefore, 38 of the evaluable patients (65.5%) had either a partial response or stable disease. Responses were seen in lung, lymph nodes, liver, soft tissue, and pleura. Thirty-three patients received post-study chemotherapy, primarily platinum-
based combination therapy. Median overall survival of all 60 patients was 10.1 months (95% CI, 7.9–13.0 months); median overall survival was 13.8 months (95% CI, 6.7–21.7 months) for partial response patients, 13.6 months (95% CI, 10.1–23.7 months) for stable disease patients, and 4.9 months (95% CI, 3.4–8.6 months) for progressive disease patients. The 1- and 2-year overall survival rates were 42.6% and 18.5%, respectively (see Fig. 1). Median progression-free survival was 5.0 months (95% CI, 3.5–6.3 months; see Fig. 2). Median duration of response was 3.3 months (95% CI, 2.7–7.1 months).

**Lung Cancer Symptom Scale.** Fifty-nine patients completed the patient LCSS at baseline. The percentage of patients considered symptomatic were as follows: anorexia, 63.7%; fatigue, 75.9%; cough, 67.2%; dyspnea, 83.1%; hemoptysis, 13.8%; and pain, 57.6%. Rates reported on the observer LCSS were similar. Fifty-five patients were included in at least one of the patient LCSS analyses. The results of the symptom items are displayed in Fig. 3. Most patients reported their symptoms as stable or improved. The highest rates of improvement were seen with anorexia, cough, and pain. The majority of patients reported no hemoptysis at baseline, so they had no opportunity to improve. The highest rate of symptoms worsening was seen with fatigue. Similar results were seen with the observer LCSS. For the patient LCSS summary items (symptom distress, interference with activity level, and global quality of life), most patients reported these as stable or improved. Patients with a partial response were more likely to be classified as improved than stable for each of the LCSS items.

**Toxicity.** All 60 patients were assessable for toxicity. Hematological toxicities by worst grade for all patients are listed in Table 2. Anemia was generally mild, with 9 patients (15.0%) requiring a blood transfusion. Grade 3 and 4 neutropenia was observed in 28.3% and 33.3% of the patients, respectively, and 9 patients (15.0%) experienced febrile neutropenia. Only 3 patients (5.0%) had grade 3/4 thrombocytopenia. There was no evidence of any cumulative hematological toxicity.

A summary of nonhematological and biochemical toxicity is listed in Table 3. The regimen was generally well tolerated, with no grade 3/4 nausea, vomiting, or sensory neuropathy. Pemetrexed-related skin rash was frequent, occurring in 23 patients (38.3%), but only 2 cases (3.3%) were grade 3. Fatigue was the most frequent nonhematological toxicity. Grade 3 fatigue occurred in 14 patients (23.3%) after a median of 3 cycles and did not appear to be related to either age or gender. One patient on long-term corticosteroids for severe lung dyspnea was diagnosed with pneumocystis carinii pneumonia at cycle 3, and two additional patients experienced documented pneumonitis of noninfectious origin. One patient experienced grade 4 diarrhea requiring hospitalization. Two patients developed pulmonary emboli, which were judged nonrelated to study medication; one resulted in death at cycle 1, and the other developed during a hospitalization for febrile neutropenia. There were no deaths attributed to chemotherapy treatment. Seven patients experienced alopecia; all but one were grade 1. Other toxicities were rare and generally mild. One patient with a history of past and present alcoholism had a grade 4 hyperbilirubinemia due to an underlying liver disorder and went off therapy at cycle 3.

**Vitamin Supplementation.** Because vitamin supplementation was complete for 47 patients, partial for 10 patients, and absent for 3 patients, we examined whether vitamin supplementation had an effect on the clinical outcome and rate of toxicities. No numerical difference (data not shown) was noticed for the response rate, overall survival, LCSS scores, median number of chemotherapy cycles administered, or toxicity rates.
DISCUSSION

Our study was designed to confirm preclinical data suggesting synergistic activity of pemetrexed and gemcitabine and to evaluate both clinical activity and tolerance of this regimen in the treatment of advanced NSCLC. The most accepted end point of patient benefit in advanced lung cancer trials is overall survival. Although there is heterogeneity in the patients enrolled in different clinical trials, the heterogeneity tends to be least in trials of chemo-naive patients and in multicenter trials. Most Phase II and III trials of standard doublet chemotherapy combinations in advanced, chemo-naive NSCLC patients show median survival times of 8–10 months. In this trial, the median survival was 10.1 months. The 1-year survival rate was 43%, the 2-year survival rate was 19%, and the 3-year survival rate was 11%. These results compare favorably with studies with the most active doublet combinations in the literature.

Response rates in advanced NSCLC have not always correlated well with patient survival and are thus not accepted as definitive evidence of patient benefit by United States regulatory agencies. In this study, the objective response rate was 15.5%, and the disease stabilization rate was 50%. This response rate is somewhat lower than that reported in many trials of other Phase II trials in which survival has been considerably more than twice the TTP, subsequent Phase III trials have failed to confirm patient benefit. In this trial, the median TTP was 5.0 months, which was approximately half of the overall median survival. This median TTP compares favorably with other doublet combinations in the literature.

active doublet combinations (20–30%). The 21% rate of disease progression compares more favorably with results from other active doublets. Otherwise, there is not a clear explanation for the lower than anticipated response rate.

Recently, a new end point of clinical benefit has emerged in the management of advanced NSCLC. As in our study, it has been seen that chemotherapy regimens with modest response profiles may be associated with prolonged survival. Carboplatin, for instance, was quoted with a low 9% response rate but was associated with longer survival than multidrug regimens (22). As demonstrated for single-agent topotecan, patients who achieved a stabilization of their disease have an overall survival identical to that of patients with a partial response (23). In our study, two-thirds of patients achieved either partial response or stable disease, and their median overall survival was identical (13.8 months for partial response patients and 13.6 months for stable disease patients). Most of these patients also experienced symptom improvement or stabilization.

Although second-line therapies can produce a small improvement in survival, the influence of second-line chemotherapy on survival in this study is not possible to evaluate (24). Assessment of clinical benefit brought by new chemotherapy should not be restricted to an evaluation of response rate and duration of survival but should also be balanced by measures of treatment-related toxicities, disease-related symptoms, and quality of life (25). Recently, the results of a randomized study comparing docetaxel with pemetrexed in the second-line setting were published (26). Pemetrexed treated patients had equivalent efficacy, as evidenced by response rates, time to progression, and survival, but with significantly reduced rates of hematologic and nonhematologic toxicity.

Assessment of lung cancer-related symptoms revealed improvements in pain, cough, and anorexia and worsening of fatigue. Evaluation of these end points is limited by the small number of patients symptomatic at baseline and by the lack of a comparison in the setting of a Phase II trial.

The pemetrexed-gemcitabine regimen was well tolerated in our experience. The only significant grade 3/4 clinical toxicities encountered in >10% of the patients were fatigue and febrile neutropenia. Fifty percent of the dose reductions occurred at cycle two. Cumulative myelosuppression was not observed. There were no severe cases of anorexia, edema, fever, or stomatitis. The only case of severe diarrhea occurred in a patient with an elevated homocysteine level. The number of patients who completed or began treatment without vitamin supplementation is too small in this study for a meaningful comparison of supplemented versus nonsupplemented patients. However, folic acid and vitamin B12 supplementation has been shown to dramatically reduce the incidence of grade 3/4 hematologic and nonhematologic toxicities in other studies (27–29). Because nearly all patients received vitamin supplementation, changes in dose or schedule would be required to reduce the rates of neutropenia.

The utility of cisplatin-free combinations in the treatment of advanced NSCLC is still a matter of debate. There is no question that cisplatin is currently the drug of choice for metastatic NSCLC (30, 31). Nevertheless, some plateau in the overall survival has been reached with the use of cisplatin-based combinations (32–36). The many toxicities of cisplatin, including severe nausea and vomiting, renal toxicity often requiring hospitalization for intravenous hydration, and long-lasting ototoxicity and neuropathy, are all detrimental to the patient’s quality of life. Furthermore, cisplatin resistance has been found to be associated with elevated excision repair complement group 1 (ERCC1) mRNA levels in tumor tissue (37, 38). High ERCC1 level has also been associated with shorter survival in NSCLC patients treated with gemcitabine plus cisplatin (39). Theoretically, NSCLC patients with high levels of ERCC1 could benefit more from effective non-platinum-based cytotoxic therapy.

Other Phase II studies of cisplatin-free regimens in NSCLC have recently been reported. The combination of gemcitabine and vinorelbine has been investigated in previously treated and untreated patients with stage IIIb and IV disease (40). In the untreated group, 16 of 42 patients (36%) experienced a partial response, median overall survival was 10.1 months, and 1- and 2-year survival was 42.9% and 31.6%. A randomized Phase II study in untreated advanced NSCLC of gemcitabine plus irinotecan or docetaxel has been conducted and reported by the Cancer and Leukemia Group B (41). In this study, gemcitabine and irinotecan produced an overall response rate of 12.8%, and gemcitabine and docetaxel produced an overall response rate of 23.1%. Median overall survival was 7.95 months and 12.8 months, respectively. Estimated 1-year survival was 23% and 51%, respectively.

To move beyond the apparent plateau in NSCLC, cytotoxic agents are being used in combination with agents having novel mechanisms of action. An example of this is the study of cisplatin, vinorelbine, and bexarotene, a novel retinoid X receptor agent, in advanced NSCLC. This regimen produced an overall response rate of 25%, a median survival time of 14 months, and 1-year, 2-year, and projected 3-year survival rates of 61%, 32%, and 30%, respectively. This apparent advance is encouraging, but due to the presence of cisplatin, this regimen would not be a treatment option for all patients. An effective, platinum-free cytotoxic regimen to be combined with such a novel agent is still needed.

Pemetrexed has now clearly demonstrated antitumor activity against NSCLC, either as a single agent or in association with cisplatin or gemcitabine (7, 9, 16, 26, 42). Evidence for non-cross-resistance of pemetrexed in NSCLC has been suggested by its activity in cisplatin-pretreated patients (42). Combination studies associating pemetrexed with other active agents, such as paclitaxel, docetaxel, irinotecan, vinorelbine, and carboplatin, are being pursued (5). Antitumor activity of these new regimens is awaited to further confirm the role of pemetrexed in the treatment of NSCLC.

Selection of day 8 pemetrexed administration was based on Phase I data of Adjei et al. (16). However, those data were produced without vitamin supplementation. A randomized, three-arm study of pemetrexed and gemcitabine is currently being conducted that should further define the optimal schedule for this combination regimen. Another Phase II/I study in NSCLC is testing the administration of these two agents on a biweekly schedule. In addition, results from a Phase I and pharmacokinetic study testing the necessity for the 90-min delay between administrations should be available in the near future.
regimen is characterized by promising overall survival, progression-free survival, and time to progressive disease, which are better indicators of efficacy than response. In addition, this regimen offers good tolerance and convenient outpatient administration. Our study showed the activity of the pemetrexed-gemcitabine combination in advanced NSCLC. Its 10.1-month median survival warrants further evaluation in a randomized fashion against the current platinum-based standards, once the optimal administration schedule is established.

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REFERENCES


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