Randomized phase II trial of gemcitabine plus weekly versus three-weekly paclitaxel in previously untreated advanced non-small-cell lung cancer


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Introduction: Gemcitabine and paclitaxel (Taxol) each provides an efficacious non-platinum option for the treatment of advanced non-small-cell lung cancer (NSCLC), but the optimal dosage and schedule of the two agents used in combination are not well defined.

Methods: Previously untreated patients with advanced NSCLC were randomized to receive gemcitabine–paclitaxel on a traditional three-weekly schedule (Arm A) or a novel weekly schedule (Arm B) as follows—Arm A (three-weekly): gemcitabine 1000 mg/m² infused >30 min on days 1 and 8 and paclitaxel 200 mg/m² infused >3 h on day 1 of a 21-day cycle or Arm B (weekly): gemcitabine 1000 mg/m² infused >30 min and paclitaxel 100 mg/m² infused >1 h, both administered on days 1 and 8 of a 21-day cycle.

Results: One hundred patients received at least one dose of treatment. The weekly schedule, Arm B, was more efficacious and less hematologically toxic than Arm A. Confirmed complete and partial response rates were 28.2% and 26.8%, respectively. Median survival was 10.3 months on Arm B and 7.9 months on Arm A (log-rank P = 0.10); 1- and 2-year survival rates also favor Arm B: 42.0% versus 34.0% and 18.0% versus 6.0%. Progression-free survival was 5.8 versus 4.8 months, again favoring Arm B (log-rank P = 0.06). There was a two-fold lower frequency of grade 3/4 hematologic events with Arm B as follows: neutropenia (16% versus 30%), thrombocytopenia (4% versus 8%), and anemia (2% versus 6%). One patient (2%) in each treatment group developed febrile neutropenia.

Conclusion: In this trial, both schedules were efficacious and tolerable, although the weekly schedule resulted in improved survival and lower hematologic toxicity compared with a three-weekly schedule. The weekly schedule of gemcitabine–paclitaxel indicates an improved therapeutic index.

Key words: gemcitabine, non-platinum doublets, non-small-cell lung cancer, paclitaxel

Introduction

The American Cancer Society predicts that 172,570 persons will be diagnosed with lung cancer during 2005, ~85% will be non-small-cell lung cancer (NSCLC), and >160,000 will die of the disease which is responsible for more cancer death than breast, prostate and colon cancer combined [1, 2]. Most patients (>80%) have locally advanced stage III or metastatic stage IV NSCLC at the time of diagnosis and are ineligible for potentially curative surgery, and 5-year survival is <10% in this patient population [3, 4]. Platinum-based chemotherapy is a standard first-line treatment of advanced NSCLC on the basis of modest improvements to survival and quality of life compared with best supportive care alone [5–8]. Several large randomized trials have compared commonly prescribed platinum doublets and found no significant efficacy differences among them [9, 10]. Non-platinum doublets can also provide modest survival benefits and improvements in quality of life, but these combinations have yet to be broadly accepted [11]. As a single agent in advanced NSCLC, gemcitabine has produced response rates of between 20% and 28% and survivals between 7 and 11 months [12–15]. Platinum combination regimens with gemcitabine have resulted in response rates between 28% and 54% and 1-year survival rates between 35% and 61%, with manageable toxicity [16–18]. The most commonly studied gemcitabine combinations in advanced NSCLC use a three-weekly schedule with gemcitabine administered at 1000 mg/m² on days 1 and 8 [19, 20]. Paclitaxel
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(Taxol, Bristol-Myers Squibb Company, New Jersey, USA) produces single-agent response rates between 20% and 42%, with 1-year survival rates of ~40% in advanced NSCLC [21–24]. Although various dosing regimens can be used, more commonly paclitaxel is administered on a three-weekly schedule. When compared with a 3-week schedule, weekly administration of paclitaxel provides greater dose intensity with similar tolerability and possible increase in efficacy [25–27].

Gemcitabine and paclitaxel have shown independent activity in advanced NSCLC, lack overlapping toxic effects, and have different mechanisms of action. Preclinical studies indicate that in combination, gemcitabine–paclitaxel could have a synergistic effect [28]. Phase I and II trials of the combination have resulted in response rates between 27% and 47%, with manageable toxicity [29–31]. Though these trials have established the feasibility of gemcitabine–paclitaxel doublets, the optimal schedule and dose in NSCLC have not been determined. No previous phase II trials compare alternate schedules of gemcitabine–paclitaxel in advanced NSCLC.

The present randomized phase II trial was designed to determine response rates, progression-free survival (PFS), median survival, and overall survival (OS) of weekly versus three-weekly gemcitabine–paclitaxel schedules among patients with advanced NSCLC as a means of selecting the best regimen for clinical practice and future phase III trials.

patients and methods

Patients in this randomized phase II study were evaluated and treated at 20 centers across the United States. The protocol was approved by the Institutional Review Board at all participating centers. All patients signed an informed consent.

patient selection

Patients with a histologically confirmed diagnosis of stage IIIB (with pleural effusion or not suitable for combined modality therapy) or IV NSCLC were enrolled in this study. All patients were required to be ≥21 years of age and have measurable disease on the basis of Response Evaluation Criteria in Solid Tumors (RECIST). Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, adequate bone marrow reserve [neutrophils > 1500 per mm³, platelets > 100 000 per mm³, hematocrit ≥ 30%, and serum transaminases ≤ 2.5 times institutional upper limit of normal (ULN)], hepatic (serum bilirubin ≤ 1.5 mg/dl times institutional ULN) and renal (creatinine clearance ≥ 50 ml/min or serum creatinine < 2 mg/dl) function, and a life expectancy of ≥3 months.

Exclusion criteria included prior chemotherapy for metastatic disease or prior radiation to the metastatic sites of interest, and any prior radiation therapy had to be completed at least 3 weeks before enrollment. Pregnant or nursing women were not eligible, and all women of childbearing potential were required to use an approved method of birth control. Patients were excluded if they had past or current history of another neoplasm other than NSCLC, significant history of cardiovascular disease, evidence of peripheral neuropathy, serious active infection, or use of any investigational agent in the month before enrollment into the study.

study design

This study was carried out in compliance with the regulatory standards of good clinical practice, the requirements of Title 21 of the Code of Federal Regulations (USA), and the principles of the Declaration of Helsinki. Patients were randomized to either a weekly or a three-weekly gemcitabine–paclitaxel schedule as follows—Arm A (three-weekly schedule): gemcitabine 1000 mg/m² infused >30 min on days 1 and 8 and paclitaxel 200 mg/m² infused >3 h on day 1 of a 21-day cycle or Arm B (weekly schedule): gemcitabine 1000 mg/m² infused >30 min and paclitaxel 100 mg/m² infused >1 h, both administered on days 1 and 8 of a 21-day cycle. Patients were pretreated with dexamethasone 20 mg i.v. or oral on day 1 and/or 10 mg on day 8 before receiving paclitaxel. Patients were also premedicated with diphenhydramine 50 mg i.v. and a Histamine H2-receptor antagonist before receiving paclitaxel.

The dose of the study drug was calculated according to the patient’s actual height and weight at the beginning of each cycle. Obviously, patients were not permitted any other chemotherapy, immunotherapy, antitumor hormonal therapy (excluding contraceptives and replacement steroids), radiation therapy, or experimental medications were permitted while the patient was on the study, but all patients received full supportive care.

Treatment of individual patients was continued with the non-platinum doublet drug combination for six cycles or until disease progression. At the investigators’ discretion, patients were treated with up to 10 cycles of the drug combination.

tumor response criteria

Standard RECIST criteria were used for classifying tumor response [32]. Complete response was defined as the disappearance of all known disease (target and non-target lesions). A partial response (PR) was defined as a 30% reduction from baseline in the sum of maximal diameters of the target lesions and a lack of disease progression in non-target lesions. Progressive disease (PD) was defined as the development of any new lesions or an increase of 20% in the maximal diameters of target lesions. Patients with stable disease (SD) did not meet the criteria for PR or PD. Confirmed responses required two observations No. <4 weeks apart. Unconfirmed response observations, which did not require confirmation, were also reported.

randomization/statistical analysis

This trial randomized 100 patients with equal probability between the two regimens. This sample size was chosen on the basis of a selection design using tumor response rate as the primary end point and assuming 45 patients per arm qualified for tumor response assessment. Patients stratification by stage of disease and gender took place at randomization to ensure balance with respect to these characteristics in the two arms. If the true response rate for one regimen was ≥10% than that of the other regimen, then there was 280% chance of correctly selecting the better regimen (on the basis of exact binomial probabilities). However, if the true response rates were nearly equal, then there was nearly an equal chance of selecting either regimen (no significance test was carried out for response rates; type-1 or ‘alpha’ error was not controlled under this design).

Statistical analyses were not stratified to avoid small numbers in the subgroups. Demographic characteristics were collected to determine the comparability of the two treatment groups. Survival was calculated from the date of enrollment to the date of death or last known contact using the Kaplan–Meier method. Estimates of 1-year and 2-year survival were computed from this curve, with 95% confidence intervals (CIs). P values were calculated using the two-sided log-rank method, where appropriate. Adverse events were assessed using the common toxicity criteria version 2.0. Grade 3/4 toxic effects were calculated as a percentage of all patients in the safety population (defined as all patients receiving at least one dose of treatment).

results

From September 2000 to August 2001, 103 patients (52 in Arm A and 51 in Arm B) were enrolled in this trial. Of these, 100
(50 in Arm A and 50 in Arm B) received at least one dose of treatment. Characteristics for these patients are summarized in Table 1. Patients in Arm A had a median age of 66 years compared with 62 years for Arm B. The percentages of patients with fully active and restricted ECOG performance status were 34% and 52% for Arm A compared with 50% and 38% for Arm B. Distribution by gender, histology, and disease stage were similar between treatment arms.

**toxicity**

One hundred patients who received at least one dose of treatment were assessable for toxicity (see Table 2). Grade 3/4 hematologic events, including neutropenia (30% versus 16%), thrombocytopenia (8% versus 4%), and anemia (6% versus 2%), occurred with a greater frequency in Arm A. Although Arm A was approximately twice as hematologically toxic as Arm B, three patients (6%) in Arm B died as a result of an adverse event compared with none in Arm A. However, there were no episodes of thrombocytopenic bleeding and no patients required platelet transfusions. One patient (2%) in each treatment group developed febrile neutropenia.

Grade 1/2 alopecia and grade 3/4 dyspnea occurred with a greater frequency (58% versus 36% and 22% versus 16%, respectively) in Arm A. Other grade 3/4 non-hematologic events occurring in ≥10% of patients in a treatment arm were pneumonia, asthenia, hypoxia, and apnea, which generally occurred with a similar frequency between groups. One patient (2%) in Arm A and none in Arm B experienced grade 3/4 rash. Constipation, vomiting, and nausea were uncommon, each occurring in ≤3% of patients overall.

**response**

Of the 100 patients included in the safety analysis, 80 (39 in Arm A and 41 in Arm B) were assessable for response (see Table 3). With regard to confirmed responses, there was one complete responder and 10 partial responders in Arm A, resulting in a confirmed response rate of 28.2% (95% CI 15.0, 44.9), and one complete responder and 10 partial responders in Arm B, resulting in a confirmed response rate of 26.8% for Arm B (95% CI 14.2, 42.9). Of the 39 assessable patients in Arm A, 16 (41.0%) had SD and 12 (30.8%) had PD. Of the 41 assessable patients in Arm B, 25 (61.0%) had SD and five (12.2%) had PD. The SD category includes five patients in Arm A and eight patients in Arm B.
patients in Arm B who had responses that were not confirmed. The overall unconfirmed response rate was 41.0% (95% CI 25.6, 57.9) in Arm A and 46.3% (95% CI 30.7, 62.6) in Arm B.

Median survival and PFS are summarized in Figures 1 and 2. These analyses were on the basis of the 100 patients comprising the safety population. In Arm A, median survival was 7.9 months (95% CI 5.0, 11.0; censorship = 2%), 1- and 2-year survival rates were 34.0% and 6.0%, and PFS was 4.8 months (95% CI 3.0, 7.5; censorship = 0%). In Arm B, median survival was 10.3 months (95% CI 6.7, 14.2; censorship = 12%), 1- and 2-year survival rates were 42.0% and 18.0%, and PFS was 5.8 months (95% CI 3.9, 10.3; censorship = 8%). Differences between treatment arms in median survival and PFS were not statistically significant, although the PFS log-rank P value was 0.06.

discussion

On this trial, weekly administration of gemcitabine–paclitaxel resulted in higher response rates, longer median survival and longer PFS than the traditional three-weekly administration schedule. The trial was designed to identify the best schedule of gemcitabine–paclitaxel for clinical use and future phase III studies and thus the statistical comparisons of median and OS for significance were not done.

While both treatment arms were generally tolerable, the weekly schedule (Arm B) was associated with lower hematological toxicity in terms of both frequency and severity. The single grade 4 hematologic toxicity of Arm B was neutropenia which occurred among only 6% of patients compared with 14% of patients on Arm A. In fact, grade 3/4 neutropenia was nearly twice as frequent in Arm A (30% versus 16%), and though uncommon in both study arms, anemia and thrombocytopenia were also more than twice as frequent in Arm A (6% and 8% versus 2% and 4%). Alopecia (38% versus 36% for grade 1/2), dyspnea (22% versus 16%), and apnea (10% versus 0%) also occurred more frequently in Arm A.

While patients in both arms had a similar distribution of gender, histology, and disease stage, differences in some baseline characteristics may have influenced the overall results of the trial. Patients in Arm B were, on average, 4 years younger than patients in Arm A. While previous studies in advanced NSCLC have shown that age does not necessarily contribute to disease progression or shorter survival time [33], one cannot rule out age discrepancy as a contributory factor to the favorable results for the weekly compared with the three-weekly administration schedule in this study. Arm B also contained a greater

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*Response analysis excluded 11 patients in Arm A (one unknown, 10 missing) and nine patients in Arm B (all missing) who were included in the safety analysis.

**Confirmed responses required two observations No. <4 weeks apart. Unconfirmed responses were on the basis of a single observation.
percentage of patients with an ECOG performance status (50% versus 34%) of 0 or 1. Nevertheless, the results of the present trial clearly favor the weekly administration schedule, and support previously published reports by Akerley et al. [25] that show a benefit in activity and tolerability with weekly administration of paclitaxel. Bhatia et al. [34] reported a phase II trial that administered gemcitabine and paclitaxel on a weekly schedule (days 1, 8, and 15 every 4 weeks). In that study, the gemcitabine–paclitaxel combination was active in advanced NSCLC, but resulted in considerable hematological toxicity. Due to toxicity, only 60% of the planned dose was administered. The authors of that study noted that elimination of day 15 gemcitabine might improve the tolerability of the schedule. The present study shows that avoiding day 15 gemcitabine and paclitaxel on Arm B reduces myelosuppression without adversely compromising the efficacy of the regimen. Treat et al. [11] reported results of a large randomized phase III study of two platinum-based regimens compared with a gemcitabine–paclitaxel regimen (administered on a three-weekly schedule as in arm A of the present study) and found no significant differences in efficacy between the platinum and non-platinum regimens. It is possible that if paclitaxel were given on the weekly schedule as in arm B of the present trial, then an increased benefit would have been observed.

The present study indicates that weekly administration of gemcitabine and paclitaxel offers optimal results of the two regimens evaluated among patients with advanced NSCLC, but confirmation in a large, prospective, randomized phase III trial setting is required. For now, the weekly regimen can be used for patient care and also provides a feasible non-trial setting is required. For now, the weekly regimen can be used for patient care.

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References


