Brief Report of Biweekly Pemetrexed and Gemcitabine in Elderly Patients with Non-small Cell Lung Cancer

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Abstract: We examined a nonplatinum-based doublet chemotherapy regimen, pemetrexed and gemcitabine given on a biweekly (every 14 days) schedule, in patients older than 70 years with newly diagnosed advanced non-small cell lung cancer. The study was closed after nine patients were treated due to excess toxicity, primarily fatigue, and nonneutropenic infection. No responses were observed. Eight of the nine patients were hospitalized during therapy and seven discontinued treatment for reasons other than progressive disease. Median progression-free survival was 1.7 months, and median overall survival was 3.9 months. We found that biweekly pemetrexed and gemcitabine was too toxic in our cohort of elderly patients with newly diagnosed advanced non-small cell lung cancer.

Key Words: Non-small cell lung cancer, Elderly, Pemetrexed, Gemcitabine.

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The median age at diagnosis with non-small cell lung cancer (NSCLC) is 70 years. Although combination chemotherapy offers a modest survival benefit in advanced NSCLC, whether this extends to elderly patients is controversial because underrepresentation in clinical trials limits evidence-based statements about this cohort. Although single agent vinorelbine improved survival over supportive care in an elder-specific randomized trial,¹ there is a lack of conclusive data regarding combination chemotherapy in elderly patients with NSCLC.²

Both pemetrexed (Alimta) and gemcitabine (Gemzar) are Food and Drug Administration-approved drugs for the treatment of NSCLC. The combination is rational because both deplete intracellular stores of deoxynucleotide triphosphates and synergistic activity is observed in preclinical models. Several phase I and phase II studies have examined the combination in NSCLC, varying the sequence and days of administration of the drugs.³⁻¹⁰ The biweekly (twice a month) regimen allows for a patient-friendly schedule and had a relatively low rate of neutropenia in phase I trials. Hence, we explored this nonplatinum-based combination as first-line therapy for elderly patients.

METHODS

This was a single institution, open-label phase II study to assess the objective response rate and safety of first-line biweekly gemcitabine and pemetrexed in patients older than 70 years with advanced NSCLC (any histology). Key inclusion criteria included performance status (PS) of 0 to 2, measurable disease, and prior definitive treatment of central nervous system metastases. The planned sample size was 55 patients, with interim analysis and stopping for lack of activity. Enrollment began on August 3, 2005. After seven patients were treated, clinical concern was raised that toxicity was higher than expected. The starting dose of both drugs was reduced; however, after two patients were treated at the lower doses without an improvement in safety, the study was closed on December 5, 2006.

Treatment was in 2-week cycles; the dose for the first seven patients was pemetrexed 500 mg/m² followed by gemcitabine 1500 mg/m² on day 1 of each cycle, and the final two patients received pemetrexed 400 mg/m² and gemcitabine 1000 mg/m². All patients received vitamin B12, folic acid, and dexamethasone as recommended with pemetrexed. Treatment continued until disease progression or unacceptable toxicity. Adverse events were graded by the NCI-CTCAE, version 3.0. Response was evaluated every 8 weeks (4 cycles). The clinical trial protocol was approved and monitored by our institutional review board. Funding was provided by Eli Lilly and Company.

RESULTS

Nine patients were enrolled, aged 70 to 82 years, including three women, six with adenocarcinoma, three with poorly differentiated carcinoma, one with central nervous system metastases, and with baseline PS of 0 (n = 2), 1 (n = 6), or 2 (n = 1). Chemotherapy cycles administered ranged from 1 to 5; four patients received only 1 cycle because of adverse events. Indeed, toxicity was the limiting factor in treatment length for most patients, Table 1. Eight of the nine...
patients were hospitalized during therapy, and only two patients discontinued protocol therapy for documented disease progression, while the remaining seven discontinued for intolerance and declining PS.

Table 2 summarizes all observed adverse events. Six of the nine patients had at least one grade 3 or greater treatment-related toxicity. Fatigue occurred in all patients. Nonneutropenic infections were noted in five patients, specifically pneumonia in three subjects and one each of urosepsis and cellulitis. Two patients died within 30 days of cycle 1; one from hemoptysis and one from respiratory failure related to pneumonia and underlying disease. Other significant treatment-related adverse events included anorexia, constipation, neutropenia, and pneumonitis.

There were no objective tumor responses by RECIST. One patient achieved a minor clinical response (patient 8), followed by 4 months of stable disease off therapy. The upper limit of the one-sided 95% confidence interval (CI) for the response rate of 0% was 28%. Power is extremely limited for survival analysis; the observed median progression-free survival was 1.7 months, 95% CI 1.5 to 2.5 months, and the median overall survival was 3.9 months, 95% CI 1.6 to 14.3 months.

**DISCUSSION**

We have demonstrated that the first-line biweekly pemetrexed and gemcitabine was poorly tolerated in a cohort of nine patients older than 70 years with advanced NSCLC. There were unacceptable levels of fatigue and infection, even in the absence of neutropenia. We had designed this phase II clinical trial to assess the response rate to biweekly pemetrexed and gemcitabine among elderly patients, but the study was closed early for intolerance. No responses were noted in the small number of patients participating, and the progression-free survival and overall survival were unusually low.
1.7 months and 3.9 months, respectively, likely influenced by two deaths during the first cycle of therapy.

The adverse events we observed tended to be multiple grade 1/2 toxicities per patient, as opposed to a primary grade 3/4 adverse event; this led to a significant proportion of the patients (seven of nine) electing to withdraw from protocol treatment before documented disease progression. In elderly patients, this is a clinically significant finding, as multiple low-grade toxicities can lead to loss of independence and decreased quality of life. Indeed, seven of our patients were hospitalized during protocol treatment, and five of these either died in the hospital that admission or were discharged to hospice or permanent nursing home placement. Undocumented disease progression may also have contributed to clinical decline in some of these patients, particularly the three that died within 2 months of elective withdrawal from protocol.

Biweekly pemetrexed and gemcitabine with the doses we used initially (500 mg/m² pemetrexed and 1500 mg/m² gemcitabine) has been studied as first-line therapy in patients with NSCLC in three other phase II trials.4–6 All had similar entry criteria to ours; two were performed in the general population and the third in either elderly (>age of 65 years) or PS 2 patients. In total, the 169 patients in these studies did moderately well, with response rates around 20% and grade 3/4 neutropenia in 25 to 45% of patients. The elderly and poor PS study did not observe increased toxicity among elderly patients but found the regimen not well tolerated by poor PS patients.5 Twenty-one-day cycle dosing of pemetrexed (500 mg/m²) and gemcitabine (1250 mg/m² days 1 and 8) has also been studied in four phase II trials comprising 319 patients with response rates ranging from 13 to 31% and grade 3/4 neutropenia in 40 to 66% of patients, higher than with the biweekly schedule.7–10 Among all seven other trials, our study seemed particularly difficult to complete with acceptable tolerance. It is difficult to interpret the precise reason for this. Perhaps our patients, although assessed as having good PS of primarily 0 or 1, were more frail than appreciated on this subjective scale. Perhaps, it was just chance that the first cohort of patients we enrolled experienced excess toxicity, or perhaps this regimen truly is too challenging for elderly patients and the other studies failed to highlight this fact given the generally younger population of patients they enrolled. In any case, our results emphasize the need to exercise caution going forward using the combination of pemetrexed and gemcitabine in patients with NSCLC older than 70 years.

The majority of the evidence guiding therapy for older patients with advanced NSCLC comes from subgroup analyses of elderly patients fit enough to enroll on age-blind randomized clinical trials.2,11 Although these have generally concluded that good PS patients older than 70 years can tolerate platinum-based doublets, ambiguity remains about how to accurately assess fitness level and about the newest regimens for NSCLC incorporating bevacizumab.12 Robust phase III elder-specific clinical trials, which tend to best represent “community” elderly patients, are few in number but have shown that single agent vinorelbine improves survival and quality of life compared with best supportive care and treatment with non-platinum-containing doublets increases toxicity compared with single agent therapy without improving efficacy.1,13 One smaller randomized trial concluded that nonplatinum combination regimens may increase survival, when compared with single agents, but it was underpowered to demonstrate this conclusively.14 Hence, the standard of care for elderly patients unable to tolerate platinum doublets remains single agent chemotherapy.2 Further investigation of nonplatinum doublets is of interest to define a “middle ground” option between mono-therapy and platinum doublets, but enthusiasm about pemetrexed with gemcitabine may be limited by the recent finding that these drugs may have preferential activity in differing histologic subgroups.15

In conclusion, we attempted to treat advanced patients with NSCLC aged 70 years and older with a biweekly regimen of pemetrexed and gemcitabine. We found that the regimen was prohibitively difficult to tolerate and closed the study after only nine patients were treated, instead of the planned 55 subjects. Our patients experienced multiple grade 1 and grade 2 toxicities, including universal fatigue, which contributed to an unacceptably high rate of hospitalization and loss of independence. This regimen should be considered with caution in elderly patients.

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REFERENCES


