A Randomized Phase II Trial of First-Line Treatment with Gemcitabine, Erlotinib, or Gemcitabine and Erlotinib in Elderly Patients (Age ≥70 Years) with Stage IIIB/IV Non-small Cell Lung Cancer

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Introduction: Single-agent gemcitabine is a standard of care for elderly patients with advanced non-small cell lung cancer, but novel therapies are needed for this patient population.

Methods: We performed a noncomparative randomized phase II trial of gemcitabine, erlotinib, or the combination in elderly patients (age ≥70 years) with stage IIIB or IV non-small cell lung cancer. Patients were randomized to arms: A (gemcitabine 1200 mg/m^2 on days 1 and 8 every 21 days), B (erlotinib 150 mg daily), or C (gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 days and erlotinib 100 mg daily). Arms B and C were considered investigational; the primary objective was 6-month progression-free survival.

Results: Between March 2006 and May 2010, 146 eligible patients received protocol therapy. The majority of the patients (82%) had stage IV disease, 64% reported adenocarcinoma histology, 90% reported current or previous tobacco use, and 28% had a performance status of 2. The 6-month progression-free survival rate observed in arms A, B, and C was 22% (95% confidence interval [CI] 11–35), 24% (95% CI 13–36), and 25% (95% CI 15–38), respectively; the median overall survival observed was 6.8 months (95% CI 4.8–8.5), 5.8 months (95% CI 3.0–8.3), and 5.6 months (95% CI 3.5–8.4), respectively. The rate of grade ≥3 hematological and nonhematological toxicity observed was similar in all three arms. The best overall health-related quality of life response did not differ between treatment arms.

Conclusions: Erlotinib or erlotinib and gemcitabine do not warrant further investigation in an unselected elderly patient population.

Key Words: Quality of life, Cumulative illness rating scale for geriatrics, Targeted therapy, Elderly.

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Lung cancer remains the leading cause of cancer mortality in the United States and the world, with approximately 85% of cases non-small cell lung cancer (NSCLC).[1–3] The majority of patients with NSCLC have advanced disease at the time of diagnosis, and the goals of treatment are to extend survival, improve health-related quality of life (HRQL), and reduce disease-related symptoms.[4,5] Many elderly patients with advanced NSCLC have significant cardiovascular and pulmonary comorbidities related to tobacco exposure and comorbidities associated with advanced age, which impacts their ability to tolerate the treatment of NSCLC. According to the Surveillance, Epidemiology, and End Results registry, the median age at the time of diagnosis of lung cancer in the United States is 69 years.[6] The definition of "elderly" has

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varied among oncology trials, but for trials of advanced NSCLC, the age ≥70 years is frequently used.[7] The number of elderly patients with advanced NSCLC is expected to increase as the size elderly population continues to increase in the next several decades.[8]

Elderly specific trials compared with age-unspecified trials recruit a more elderly population; among elderly patients in elderly specific trials compared with age-unspecified trials, a lower rate of grade ≥3 toxicities is observed.[9] Several elderly specific phase III trials in advanced NSCLC had been performed when this trial was designed. Single-agent vinorelbine was compared with best supportive care ($n = 161$), and patients assigned to the vinorelbine arm experienced longer survival, improvement in quality of life (Qol) functioning scales, and fewer lung cancer-related symptoms.[10] A subsequent phase III trial ($n = 698$) compared single-agent vinorelbine or gemcitabine with the combination of gemcitabine and vinorelbine; the combination was not more effective than single-agent vinorelbine or gemcitabine.[11] The Qol was similar in all three treatment arms but a higher rate of toxicity was observed in the combination arm. A smaller phase III trial ($n = 120$) compared vinorelbine with the combination of gemcitabine and vinorelbine; the combination was associated with superior survival and a delay in symptom and Qol deterioration.[12] When this trial was designed, single-agent vinorelbine or gemcitabine were considered standard therapies for elderly patients with advanced NSCLC.

A single-arm phase II trial of erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), in elderly patients with advanced NSCLC had revealed promising survival and a low rate of toxicity.[13] A single-arm phase II trial of docetaxel and gefitinib in elderly patients with advanced NSCLC revealed acceptable toxicity and promising efficacy.[14] The combination of gemcitabine and erlotinib compared with single-agent gemcitabine had revealed superior survival in patients with advanced pancreatic cancer;[15] of the patients enrolled in the gemcitabine and erlotinib arm, 80% received an erlotinib dose of 100 mg daily. Data reporting the efficacy and toxicity of gemcitabine and erlotinib in advanced NSCLC were not available when this trial was designed and the role of EGFR mutations in the selection of patients for EGFR TKI therapy was not known when this trial was designed. We designed a randomized phase II trial to investigate the activity of erlotinib alone and in combination with gemcitabine in elderly patients with advanced NSCLC.

PATIENTS AND METHODS

Eligibility Criteria

Patients were required to have a histologic or cytologic diagnosis of stage IIIB or IV NSCLC (all histologies), aged ≥70 years, and have an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2. Patients could not have received treatment for metastatic NSCLC; patients could have received prior adjuvant chemotherapy, but time since prior adjuvant chemotherapy was required to be ≥1 year. Patients were required to have adequate hematological function (defined as absolute neutrophil count [ANC] ≥1500/mm^3, platelets count ≥100,000/mm^3, hemoglobin ≥8.0 g/dl), hepatic function (defined as aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 × upper limit of normal [ULN], alkaline phosphatase [AP] ≤4 × ULN, and total bilirubin ≤ULN), and renal function (defined as serum creatinine ≤1.5 × ULN). Patients were required to have evaluable disease by RECIST.[16] Patients with asymptomatic treated brain metastases were eligible. Patients with a history of severe hypersensitivity reactions to gemcitabine, incompletely healed from previous oncologic or major surgery, unable to participate in the HRQL questionnaires or provide informed consent were ineligible. This trial was reviewed and approved by the institutional review board of all the participating centers, and patients were required to provide informed consent before any study related tests were performed. The study was registered with ClinicalTrials.gov (NCT00283244).

Treatment

Patients assigned to arm A received gemcitabine 1200 mg/m^2 intravenously on days 1 and 8 every 21 days until disease progression, unacceptable toxicity, or a maximum of four cycles. At the time of disease progression, patients were offered erlotinib 150 mg orally daily until disease progression or unacceptable toxicity. Patients assigned to arm B received erlotinib 150 mg orally daily until disease progression or unacceptable toxicity, and patients assigned to arm C received gemcitabine 1000 mg/m^2 intravenously on days 1 and 8 every 21 days in combination erlotinib 100 mg daily. In arm C, patients received gemcitabine until disease progression, unacceptable toxicity, or for a maximum of four cycles; after four cycles of gemcitabine, patients continued single-agent erlotinib until disease progression or unacceptable toxicity. Patients in arm C could undergo dose escalation of erlotinib to 150 mg daily in cycle 2 at the discretion of the treating physician if no grade ≥2 or higher toxicity typical of erlotinib was observed during the first cycle. In all three treatment arms, 21 days was considered one cycle.

For patients who experienced grade 3 rash or diarrhea related to erlotinib, treatment was interrupted until toxicity resolved to grade ≤1 and then resumed erlotinib with a 50 mg dose reduction. For the second episode of grade 3, rash or diarrhea the erlotinib dose was reduced to 50 mg in arm B and 25 mg in arm C. Patients discontinued study treatment if they developed grade 4 rash, diarrhea, or possible interstitial lung disease.

Patients were required to have an ANC ≥1500/mm^3 and a platelet count ≥100,000/mm^3 before the next cycle; if the ANC or platelets were below the threshold, they were checked weekly. If ANC and platelets were not within acceptable limits after more than 2-week delay, the patient discontinued study treatment. If a patient experienced febrile neutropenia, an ANC less than 500/mm^3 for ≥5 days, or platelet count less than 50,000/mm^3, the gemcitabine dose in arm A was reduced from 1200 mg/mm^3 to 900 mg/m^2: in arm C, the gemcitabine dose was reduced from 1000 to 800 mg/m^2. For day 8 gemcitabine treatment, patients were required to have an ANC ≥1000/mm^3 and a platelet count more than 75,000/mm^3 to receive the full dose of gemcitabine; patients with ANC of 500 to 999/