Original Study

Patients Treated With Platinum-Doublet Chemotherapy for Advanced Non–Small-Cell Lung Cancer Have Inferior Outcomes If Previously Treated With Platinum-based Chemoradiation

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Abstract

We performed a retrospective study of NSCLC patients treated with carboplatin and gemcitabine chemotherapy for either de-novo metastatic disease or recurrent disease after platinum-based chemo-radiation and determined that outcomes are inferior in patients previously exposed to platinum during chemo-radiation. These results suggest that non platinum-based agents or targeted therapies should be considered in this group.

Introduction: The standard of care for locoregionally advanced non–small-cell lung cancer is concurrent platinum-based chemoradiation. Many patients relapse, and subsequent systemic treatment may involve platinum-doublet chemotherapy. It is not known if prior platinum-based chemoradiation influences the response to platinum-based chemotherapy given subsequently for relapse. Therefore, we compared outcomes in these patients with those in patients without prior treatment. **Methods:** A retrospective study of patients who had been treated with carboplatin and gemcitabine chemotherapy for de novo metastatic disease or recurrent non–small-cell lung cancer after receiving platinum-based chemoradiation. The primary outcome was progression-free survival (PFS). **Results:** A total of 104 patients were analyzed. The median age was 63 years (range, 35-81 years), with 63 (61%) patients with newly diagnosed disease and with 41 (39%) who were previously treated. The response rate was significantly lower for those previously exposed to chemoradiation (10% vs. 29%: $P = .001$), as was the median PFS (3.6 months vs. 5.7 months; $P = .002$), and median overall survival (OS) (8.6 months vs. 12.1 months; $P = .007$). Only the treatment group was a significant predictor ($P = .032$) of PFS by univariate analysis. In univariate analysis; sex (men; $P = .04$), histology (squamous cell; $P = .04$), Eastern Cooperative Oncology Group Performance Status Scale ($P = .002$), and treatment group ($P = .023$) predicted significantly inferior OS. Multivariate analysis showed that performance status was the only significant predictor of inferior OS. **Conclusion:** Outcomes were inferior in patients previously exposed to platinum-based chemoradiation. An approach of stratifying such patients in future trials of chemotherapy should be adopted. Alternative options such as non–platinum-based agents or targeted therapies should be considered in this group.

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Introduction

Dissemination of non–small-cell lung cancer (NSCLC) can be diagnosed either de novo in untreated patients at presentation or after previously attempted curative treatment of locoregional disease. Regardless, the standard of care in patients whose tumors lack a targetable mutation is the same in both settings: chemotherapy,

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which could consist of a platinum-based doublet, a nonplatinum doublet, or a nonplatinum single agent. Supporting this is the observation by Sekine et al[1] that responses to chemotherapy were similar in patients diagnosed with stage IV NSCLC de novo compared with patients who had recurred after previous surgical resection, although survival was superior in the patients who had postoperative recurrence.[1]

However, the curative treatment of previously untreated locoregional disease now frequently involves the use of chemotherapy, usually platinum based, either as an adjuvant after surgery or given concomitantly with high-dose radiotherapy.[2] In theory, patients who were initially treated with a platinum agent as part of chemoradiotherapy (CRT) and then relapse may have been left with a clonal population of malignant cells that are platinum resistant.[3] This could potentially mean that patients who relapsed and who are re-treated with platinum-based chemotherapy may not achieve the same degree of benefit as those who receive platinum-based chemotherapy as their first-line treatment.

In a small retrospective study of patients treated with first-line chemotherapy, rechallenge on relapse with the same chemotherapy (usually platinum based) to which the patients had originally responded resulted in a response rate of 29% and superior survival compared with a cohort of patients treated with a second-line agent (docetaxel), which suggests that, in this setting, rechallenge with the first-line agents is a reasonable strategy rather than switching to a different drug.[4] Because we were unable to find comparable data in patients who relapsed after prior CRT, we undertook this retrospective study to determine if the limited chemotherapy administered during CRT had an impact on subsequent response and survival when patients were rechallenged with platinum-based chemotherapy compared with patients with no prior platinum exposure.

Materials and Methods

Eligibility Criteria

Sequential patients with a pathologic diagnosis of NSCLC who were treated with palliative carboplatin and gemcitabine chemotherapy for metastatic or locally recurrent NSCLC between January 1, 2002, and December 31, 2006, were included. Patients were divided into 2 groups:

Group A. Patients with newly diagnosed metastatic NSCLC who had not received any previous treatment.

Group B. Patients with NSCLC who were previously exposed to platinum-based chemotherapy as part of CRT.

Due to small numbers and heterogeneous data, a third group of patients previously treated with radiation alone or non−platinum-based chemoradiation were not included. The patients were generally treated with a standard protocol of carboplatin (AUC 5) day 1 and gemcitabine (1000 mg/m^2) day 1 and 8 of a 21-day cycle. All patients treated with at least 1 cycle of chemotherapy were analyzed.

Evaluation

All relevant medical information was obtained from the hospital medical records after approval of the project by the hospital ethics committee. The primary objective was to compare the progression-free survival (PFS) of group A and group B from the time of commencement of treatment with palliative carboplatin and gemcitabine chemotherapy for metastatic or locally recurrent disease. Secondary objectives were to compare the 2 groups with respect to response rate, clinical benefit rate (complete or partial response or stable disease), the time to progression, and overall survival (OS). Scans were routinely performed after every 2-3 cycles of chemotherapy, and tumor response was determined by using the Response Evaluation Criteria in Solid Tumors by computed tomography.[5]

PFS time was defined as the time from the commencement date of palliative carboplatin and gemcitabine to subsequent progression or death without prior progression. OS was defined as the time from the start of therapy with palliative carboplatin and gemcitabine to documented death due to any cause. Both time-to-event variables were censored by the study cutoff date (April 1, 2010).

Statistical Analysis

PFS and OS were estimated by using Kaplan-Meier algorithms. Because the proportional hazards assumption was not satisfied, the Wilcoxon test for comparing the survival curves was used instead of the log-rank test. Univariate and multivariate analyses of prognostic factors were performed by using Cox regression to examine differences with respect to PFS and OS for each of the groups. The Fisher exact test was used to compare both the tumor response rate and the clinical response rate to chemotherapy between the 2 groups. Logistic regression was used to compare the clinical benefit rate for each group by adjusting for significant prognostic factors. Values of $P < .05$ were considered statistically significant. Statistical calculations were performed by using SPSS version 18.0 (SPSS Inc, Chicago, IL).

Results

A total of 104 patients treated from January 1, 2002, to December 31, 2006, were identified, with 63 (61%) patients in group A and 41 (39%) in group B. The median age was 63 years (range, 35-81 years) with 71 (68%) men and 33 (32%) women. Baseline characteristics were similar in each group (Table 1). The median follow-up at the study censor date was 68 months (range, 6.5-108 months). In group B, a variety of chemotherapy regimens were used concomitantly with radiotherapy, which was given as a potentially curative treatment to the primary site and involved regional lymph nodes after appropriate staging, including a positron emission tomography, which included carboplatin and paclitaxel in 17 patients, single-agent carboplatin in 12 patients, cisplatin and vinorelbine in 7 patients, cisplatin and gemcitabine in 2 patients, single-agent cisplatin in 1 patient, and cisplatin and 5-fluorouracil in 1 patient. All of these regimens involved low-dose weekly chemotherapy given during CRT, with no patient who received full-dose systemic therapy. No additional chemotherapy was given before or after CRT.

Sixty-seven (64%) patients received more than 3 cycles of carboplatin and gemcitabine chemotherapy. Second-line systemic therapy was received by 63.5% of group A (n = 40) and 53.7% of group B (n = 22). Agents included docetaxel (group A, 20.6% [n = 13]; group B, 19.5% [n = 8]), pemetrexed (group A, 20.6%; group B, 12.1%), and erlotinib (group A, 9.5% [n = 6]; group B, 7.3% [n = 3]). Of group A, 28.5% (n = 18), and, of group B, 19.5% (n = 8) had third-line therapy. Because epidermal growth