Estimated Creatinine Clearance Rate Is Associated With the Treatment Effectiveness and Toxicity of Pemetrexed As Continuation Maintenance Therapy for Advanced Nonsquamous Non–Small-Cell Lung Cancer

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Abstract

The purpose of this study was to explore the predictive factors of the effectiveness and treatment toxicity for pemetrexed as continuation maintenance therapy in patients with advanced nonsquamous non–small-cell lung cancer. Patients with an estimated creatinine clearance rate (Ccr) < 60 mL/min had a significantly longer survival. However, a decrease in estimated Ccr was associated with a increased risk of Grade 3/4 neutropenia and anemia.

Background: The purpose of this study was to explore the predictive factors of the effectiveness and treatment toxicity for pemetrexed as continuation maintenance therapy in patients with advanced nonsquamous non–small-cell lung cancer (NSCLC). **Patients and Methods:** Patients with advanced nonsquamous NSCLC treated with pemetrexed as continuation maintenance therapy were enrolled. The medical records were reviewed and analyzed, including data on basic characteristics, estimated creatinine clearance rate (Ccr), treatment responses, progression-free survival (PFS), overall survival (OS), and treatment-related toxicities. **Results:** A total of 124 patients were included and all had adenocarcinoma. Patients with an estimated Ccr $<$ 60 mL/min had a significantly longer PFS and OS ($P = .045$, and $P = .006$, respectively). Each 10 mL/min increase in estimated Ccr was associated with an increase of 9.8% in the risk of disease progression, and an increase of 9.2% in the risk of death. In contrast, an increase of 10 mL/min in estimated Ccr was associated with a decreased risk of Grade 3/4 neutropenia by 50.9% and anemia by 42.2%. **Conclusion:** Estimated Ccr is helpful in predicting the effectiveness and treatment toxicities of pemetrexed maintenance therapy.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Platinum-based chemotherapy is recommended as first-line treatment for advanced non–small-cell lung cancer (NSCLC), which might prolong survival and improve quality of life.[1] Although improvement has been achieved over the past decades, median progression-free survival (PFS) was 3 to 5 months for first-line platinum-based chemotherapy and median overall survival (OS) remained at 7 to 10 months.[2,3]

Many efforts were made to improve the survival benefit of first-line chemotherapy for patients with advanced NSCLC. A meta-analysis of randomized trials demonstrated that extending

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chemotherapy could substantially improve PFS, with a modest improvement in OS and a greater rate of adverse events.[4] Maintenance therapy is another strategy to improve outcomes for patients with advanced NSCLC.[5-8] After achieving disease control, maintenance therapy is to prolong treatment duration at the end of initial chemotherapy,[5,6] with adding either the drugs included in the induction chemotherapy regimen (continuation maintenance) or other not cross-resistant agents (switch maintenance).[7,8]

The treatment guidelines of the American Society of Clinical Oncology[9] and European Society of Medical Oncology[10] suggest maintenance therapy for patients with advanced nonsquamous NSCLC who did not have disease progression immediately after platinum-based chemotherapy. Several phase III clinical trials demonstrated that maintenance therapy might improve PFS and OS for advanced NSCLC patients with controlled disease after 4 cycles of platinum-based chemotherapy,[11-15] including the maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT) trial for pemetrexed as continuation maintenance therapy. Compared with the best supportive care, pemetrexed maintenance therapy significantly improved PFS, OS, and quality of life.[13-15] A good safety profile was also presented in pemetrexed maintenance therapy.[16,17]

Compared with studies on first-line or second-line therapy in NSCLC, few studies evaluated the predictive factors of the effectiveness of pemetrexed as maintenance therapy. Therefore, we conducted a retrospective study to explore the clinical factors potentially associated with the outcome and treatment toxicities of pemetrexed as continuation maintenance therapy for patients with advanced nonsquamous NSCLC.

Patients and Methods

Patients

From September 2009 to September 2012, patients with stage IIIB or IV nonsquamous NSCLC treated with pemetrexed as continuation maintenance therapy and with Eastern Cooperative Oncology Group Performance Status of 0 to 1 were included. These patients were recruited from National Taiwan University Hospital and National Taiwan University Hospital Yunlin Branch. All patients had received 4 to 6 cycles of pemetrexed with platinum as first-line chemotherapy without disease progression. The doublet regimens were pemetrexed (500 mg/m^2) with cisplatin (60-75 mg/m^2) or carboplatin (Area under the curve 4-6) on day 1 every 3 weeks. The patients received pemetrexed 500 mg/m^2 intravenously every 3 weeks as continuation maintenance therapy.

The medical records were reviewed and data on age, sex, smoking status, comorbidities, disease stages, metastatic sites, cisplatin or carboplatin use, previous or concurrent palliative radiotherapy, treatment responses to first-line chemotherapy and maintenance therapy, survival, and chemotherapy-related hematologic, hepatic, and renal toxicities were analyzed. Disease stages were determined according to the seventh version of the tumor, node, metastases staging system for lung cancer of the International Association for the Study of Lung Cancer.[18] The reasons for treatment discontinuation during the follow-up period were recorded.

The estimated creatinine clearance rate (Ccr) was calculated using the Cockcroft–Gault formula at the first dose of pemetrexed maintenance therapy. According to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guideline for evaluation, classification, and stratification of chronic kidney disease[19] and the BIRMA (Belgian Renal Insufficiency and Anticancer Medications) study,[20] a creatinine level > 1.2 mg/dL,[20] or an estimated creatinine clearance < 60 mL/min[19,20] is a sign of renal insufficiency. Therefore, the cutoff value for categorizing serum creatinine as < 1.2 or ≥ 1.2 mg/dL and for categorizing estimated Ccr as < 60 or ≥ 60 mL/min was used.

Evaluation of Treatment Effectiveness and Toxicities

Chest radiography was performed every 2 to 4 weeks, and chest computed tomography scans were undertaken every 2 to 3 months as routine clinical practice, and as needed to confirm the treatment response. Treatment response was defined as the best response recorded during the period from the start of the treatment to the time of disease progression or treatment discontinuation. The treatment responses were evaluated according to the Response Evaluation Criteria in Solid Tumors[21] and defined as complete remission (CR), partial response (PR), stable disease (SD), and progressive disease. Response rate was defined as the percentage of patients who achieved CR or PR.

Information on survival was obtained through active follow-up based on verification of the patients' vital status. The definition of PFS was defined as the time period from the date of beginning pemetrexed maintenance therapy to the date of objectively determined disease progression. Patients who had not experienced disease progression but discontinued treatment because of unacceptable adverse events, decision of the patient or physician, or died were censored. OS was defined as the time period from the date of beginning pemetrexed maintenance therapy to the date of death or the last follow-up. Patients were followed until July 31, 2013.

Any Grade 3 to 4 hematologic, hepatic, or renal toxicities that occurred during the period of pemetrexed maintenance therapy were recorded, and if the patients discontinued pemetrexed maintenance therapy because of intolerable adverse effects. The adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.[22]

Statistical Analysis

Continuous variables are expressed as median with ranges, and categorical variables as a percentage of the group from which they were derived. The proportions of variables between groups were compared using Pearson χ^2 test or Fisher exact test. Kaplan–Meier curves were plotted for the subgroups of clinical factors, and the log-rank test was used to determine statistical significance. A Cox regression model was used for covariate analysis to determine the hazard ratio (HR) of clinical factors and survival. A P value $< .05$ was considered significant. Multivariate analysis using a logistic regression model was performed with variables with a P value $< .05$ in univariate analysis. All analyses were performed using SPSS software (version 16, SPSS Institute, Chicago, IL).