Costs and Clinical Outcomes among Patients with Second-Line Non-small Cell Lung Cancer in the Outpatient Community Setting

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Introduction: A comparison of clinical and economic outcomes among patients receiving second-line monotherapy with erlotinib, docetaxel, and pemetrexed for non-small cell lung cancer was conducted using a large network of outpatient community clinics.

Methods: We identified 610 patients with advanced non-small cell lung cancer who received 2L treatment from July 1, 2006, to June 30, 2008, and were followed up through July 1, 2009, to evaluate progression-free survival (PFS), overall survival (OS), costs, and health resource utilization. Cox proportional hazards regression were used to compare PFS and OS across treatment cohorts. Economic outcomes were calculated per patient per month (PPPM) during a 12-month follow-up period.

Results: There were 73 patients who received erlotinib, 87 received docetaxel, and 450 received pemetrexed. The median age was 67 years, and 55% were men. No significant differences in stage, baseline performance status, hemoglobin level, or body mass index were observed by treatment. The median OS was 132 days for docetaxel, 132 days for pemetrexed, and 155 days for erlotinib ($p = 0.39$). Adjusting for age, gender, stage, performance status, and hemoglobin level, there was no significant association between treatment type and OS ($p = 0.36$) or PFS ($p = 0.26$). Relative to pemetrexed, total adjusted costs PPPM was $1579 lower for docetaxel and $1584 lower for erlotinib ($p < 0.05$). Outpatient visits, laboratory procedures, and acute care visits were also less frequent with erlotinib relative to pemetrexed (−2.6 PPPM, $p < 0.05$).

Conclusions: We observed no significant differences in OS and PFS between patients receiving erlotinib, docetaxel, and pemetrexed. Nevertheless, erlotinib and docetaxel were associated with a statistically significant lower costs and resource use relative to pemetrexed.

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In the United States, lung cancer is the second most common cancer in both men and women, accounting for 15% of all new cancers, and is the leading cause of cancer deaths.[1] Non-small cell lung cancer (NSCLC) comprises approximately 85 to 90% of all lung cancer cases, and more than half are diagnosed at advanced stage, which carries an overall 5-year survival rate of 15%.[1,2]

Patients with advanced NSCLC typically receive first-line chemotherapy with or without bevacizumab. Second-line therapy is recommended in patients who experience disease progression during or after first-line therapy and who have good performance status.[3–7] Second-line therapy has demonstrated an increase in survival and reduction in deterioration of symptoms and quality of life among patients with metastatic lung cancer.[8–14]

The current FDA-approved second-line treatments for advanced NSCLC include intravenous docetaxel, intravenous pemetrexed, and oral erlotinib—an epidermal growth factor receptor tyrosine kinase inhibitor. These three agents differ with respect to mechanism of action, method of administration, and adverse event (AE) profile,[15–17] but all have demonstrated a benefit of similar magnitude and have acceptable cost-effectiveness ratios (compared with best supportive care) in the United States.[10,12–14,18,19] Economic models and cost comparisons of these second-line agents have been published[20–24] although two of these analyses were based on clinical trial data that do not record costs directly or may have excluded some patients who should be included in cost comparisons.[20,22]

The first head-to-head randomized clinical trial comparing the efficacy and safety of erlotinib versus docetaxel and pemetrexed has reported a similar overall survival (OS) rate between all three agents in second-line NSCLC.[25] The tolerability profile of erlotinib[14,26] has been shown to be more favorable compared with docetaxel[11–13] and pemetrexed.[12,26] Nonhematologic AEs such as pulmonary toxicities, infection, nausea, and vomiting were more common in chemotherapy,[11–13,26] whereas erlotinib patients had higher incidence of weight loss, rash, and diarrhea.[14,26] These AEs may translate to higher cost of care in the real-world setting if patients require routine prophylaxis to prevent or reduce drug-induced adverse effects.

Electronic medical records (EMR) data are accumulating to enable real-world comparisons of these agents. The goal of this study was to describe clinical and economic outcomes among patients receiving second-line therapies for NSCLC in a large network of outpatient community clinics in the United States.

PATIENTS AND METHODS

Data Source

This study used clinical data from US Oncology's iKnowMed (iKM) oncology-specific EMR system. This system captures demographic, clinical, and treatment data for patients receiving care within the US Oncology's network of approximately 1200 community-based oncologists. During the study time period, the iKM EMR system was implemented across approximately 82% of the US Oncology network. To estimate cost of care and resource utilization, we linked patients with NSCLC identified in iKM EMR to US Oncology's Claims Data Warehouse (CDW). Using current methodology, we were able to link greater than 92% of the patients in iKM to CDW. The CDW repository houses all claims for services provided within the US Oncology network. Data include charge code (HCPCS/CPT) and descriptions, date of service, quantity, amount billed, and primary payer. Pharmacy data from Care Advantage Specialized Pharmacy and on-site pharmacies were used to evaluate treatment patterns and cost. Data were deidentified and accessed in compliance with the Health Insurance Portability and Accountability Act. The institutional review board at US Oncology approved the use of institutional patient data for this study.

Study Population

We identified 1294 patients with advanced NSCLC who received second-line chemotherapy regimens in the 22-month period from July 1, 2006, to April 30, 2008. Patients were excluded from the analysis if they were enrolled in clinical trials ($n = 104$), received concurrent treatment for another cancer during the study period ($n = 90$), EMR data did not link to CDW ($n = 78$), and they were not treated with erlotinib, pemetrexed, or docetaxel or unable to link pharmacy data ($n = 412$). Of the 610 patients who meet the inclusion criteria for the study, 73 (12%) were in the erlotinib group, 450 (74%) in pemetrexed, and 87 (14%) in docetaxel. Patients were followed up through June 30, 2009, date of death, or last follow-up date for the purposes of evaluating patterns of care and outcomes. The minimum potential follow-up was 14 months with a maximum of 36 months.

Study Variables

Patient characteristics abstracted from iKM included age, gender, stage at diagnosis, baseline hemoglobin levels, and performance status. Hemoglobin levels were measured before initiation and after completion of first-line chemotherapy. Treatment characteristics included dose and duration of first-line chemotherapy. Documented survival status in iKM was supplemented with data from the Social Security Death Master File to identify additional decedents. Approximately 20% of recorded deaths were supplemented by the Social Security Death Master File.

For estimating progression-free survival (PFS), disease progression is identified by an escalation in line of therapy (LOT). For example, after the completion of first-line therapy, date of disease progression is identified as the date that a patient progresses to second-line therapy. Escalation in LOT is documented in a standardized fashion in iKM (i.e., selection from a "drop down" menu). Further, treatment discontinuation and the reason for treatment discontinuation are also captured in iKM and allow differentiation of patients who have escalated their LOT versus those who have discontinued therapy due to tolerability issues. Although the gold standard for identifying PFS would include radiologic or clinical evidence of disease progression, escalation in LOT is a reasonable proxy for disease progression.

Economic outcomes derived from outpatient claims and pharmacy data included total outpatient, chemotherapy, supportive care costs, and frequency of outpatient physician visits, laboratory procedures, and acute care (ER/inpatient) visits. Costs were considered from a payer's perspective and derived from outpatient claims data in CDW.

Statistical Analysis

Patients were described at baseline with respect to demographic and clinical characteristics overall and stratified by treatment cohort. The Kaplan-Meier method and corresponding log-rank tests were used to estimate and compare differences in PFS and OS across treatment cohorts. Based on an intent-to-treat analysis, Cox proportional hazards regression was used to evaluate PFS and OS across treatment cohorts. Age, gender, stage at diagnosis, baseline performance status, body mass index, and hemoglobin were covariates included in the model.

Costs were estimated based on unadjusted 2007 Medicare reimbursement rates, Geographic Practice Cost Index 93. Although reimbursement rates were available for the large majority (97%) of charges, for the remaining charges missing a Medicare rate (predominately G codes and E&M codes), we imputed costs using a median charge to cost ratio that was calculated using all codes for which Medicare reimbursement were available. Costs were calculated using a standard cost per patient per month (PPPM) metric. For months in which a patient did not accrue costs, a value of zero was applied to ensure that those patient-months were included in the denominator for the cost PPPM calculations. We did not perform log transformation of costs as costs were already normally distributed and log transformation resulted in nonnormal distribution. Costs for oral chemotherapy agents were estimated by applying Wholesale average costs to those patients with documented orders for these agents. Because of the short timeframe of the study, discounting was not applied. Costs were also not adjusted to increases in the consumer product index as the distribution of patients in each treatment category was relatively constant during the study time period. Multiple regression analyses were used to estimate the inde-

