Original Study

Relationship of Driver Oncogenes to Long-Term Pemetrexed Response in Non–Small-Cell Lung Cancer

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Abstract

In this retrospective study, patients with non–small-cell lung cancer (NSCLC) were selected to receive pemetrexed for more than 12 months to identify which clinicopathologic characteristics were associated with long-term disease control. Tumors with *ALK* and *ROS1* gene rearrangements were overrepresented compared with a general NSCLC adenocarcinoma population. Patients with *EGFR, ALK, ROS1, KRAS,* and *NRAS* oncogenic driver mutations had improved outcomes.

Background: Pemetrexed is approved in the treatment of advanced stage nonsquamous non–small-cell lung cancer (NSCLC). The length of response is variable, and we thus sought to identify which clinicopathologic characteristics are associated with long-term disease control with pemetrexed. **Patients and Methods:** Patients with metastatic NSCLC received pemetrexed (with or without bevacizumab) for 12 months or longer, either as maintenance treatment after first-line platinum-based chemotherapy or as subsequent treatment. Clinical and pathologic characteristics were collected. **Results:** Of a total of 196 patients who received pemetrexed starting in 2007, 25 patients were identified who received pemetrexed for over 1 year. Of these, 15 patients received pemetrexed with or without bevacizumab as maintenance treatment and 10 patients received pemetrexed as subsequent treatment. Fifteen (60%) of 25 patients had an oncogenic driver mutation as follows: 5 (20%) had *ROS1* gene rearrangements, 4 (16%) had *ALK* gene rearrangements, 3 (12%) had *KRAS* mutations, 2 (8%) had epidermal growth factor receptor (*EGFR*) mutations, and 1 (4%) had an *NRAS* mutation. The median overall survival was 42.2 months (95% confidence interval, 37.4-61.3) and median progression-free survival was 22.1 months (95% confidence interval, 15.1-29.1). Patients with an oncogenic driver mutation had significantly better progression-free survival ($P = .006$) and overall survival ($P = .001$). **Conclusion:** Among patients with NSCLC who received pemetrexed for an extended time, those with *ALK* and *ROS1* gene rearrangements were proportionally overrepresented compared with that anticipated in a general nonsquamous NSCLC population, and patients with oncogenic driver mutations had improved outcomes.

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Introduction

In the treatment of metastatic non–small-cell lung cancer (NSCLC), palliative chemotherapy has 1-year survival rates of 30% to 40%.[1,2] Historically, first-line chemotherapy was administered for 3 to 4 months, followed by a period of observation, given the limitations of cumulative drug toxicity. Pemetrexed is approved by the United States Food and Drug Administration for treatment of patients with nonsquamous NSCLC as single agent second-line treatment,[3] first-line treatment in combination with platinum,[2] and for maintenance therapy after first-line platinum-based chemotherapy.[4,5] Unlike most other cytotoxic chemotherapeutic agents used in NSCLC, pemetrexed is relatively well tolerated at full doses despite long-term administration without a drug holiday.

Continuing pemetrexed as maintenance therapy, either after first-line platinum or as monotherapy in subsequent treatment lines, is increasingly in common clinical practice. An overall survival (OS)

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and progression-free survival (PFS) benefit was established for maintenance pemetrexed after cisplatin therapy in the PARAMOUNT [5] study, and the AVAPERL[6] study demonstrated that maintenance pemetrexed and bevacizumab therapy was superior to maintenance bevacizumab therapy alone after cisplatin-based first-line therapy.

In these trials, as well as the JMEN,[4] PointBreak,[7] and JMEI[3] trials of pemetrexed, some patients continued to receive pemetrexed-based therapy without disease progression for more than 12 months, but the molecular characteristics of their tumors were not described. Because tumors are now routinely tested at least for epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) gene rearrangements, the interaction between these favorable driver oncogenes and the duration of pemetrexed benefit is of clinical interest. Initial reports suggested that the PFS on pemetrexed in metastatic NSCLC patients is significantly longer among those harboring *ALK* gene rearrangements than those without, with a median PFS of about 9 months.[8,9] In a subsequent, larger retrospective study,[10] the median PFS of patients with *ALK*-positive tumors was more modest—8.5 months when administered as a platinum-based doublet and 4.4 months as a single agent in the second- and third-line setting compared to *KRAS,* which showed a relatively shorter median PFS of only 4.2 months as first-line combination therapy but had a longer 7.8-month PFS in the setting of second- and third-line monotherapy. In phase 3 trials of first-line[11] and second-line[12] crizotinib studies versus chemotherapy in *ALK* arrangement NSCLC patients, pemetrexed had an intermediate PFS of 7.0 and 7.7 months, respectively. A recent case series from our institution suggested that some lung adenocarcinoma patients whose tumors harbored the *ROS1* gene rearrangements also had a prolonged PFS when treated with pemetrexed.[13] Interestingly, the outcomes of *EGFR*-mutant patients have not been reported as an independent subgroup with regard to long-term pemetrexed therapy. Together, these prior studies suggested a potential interaction between pemetrexed response and molecular features of NSCLC. In the current retrospective study, patients were selected who were treated with pemetrexed for more than 12 months sequentially, with or without bevacizumab, to determine which clinicopathologic characteristics were associated with long-term disease control.

Table 1 Patient and Tumor Characteristics

Characteristic	Value
Gender	
Male	7 (28%)
Female	18 (72%)
Age (years)	
Median	60
Range	19-82
<60 years	12 (48%)
≥60 years	13 (52%)
Smoking Status	
Former or current smoker	12 (48%)
Never smoker	13 (52%)
WHO Performance Status	
0	3 (12%)
1	20 (80%)
2	2 (8%)
Stage	
Stage IV	20 (80%)
Recurrent/metastatic	5 (20%)
Histology	
Adenocarcinoma	23 (92%)
NSCLC, NOS	2 (8%)
Ethnicity	
Asian	7 (28%)
Non-Asian	18 (72%)
Site of Metastasis	
Pleural effusion	5 (20%)
Lung metastasis	14 (56%)
Adrenal metastasis	4 (16%)
Liver metastasis	4 (15%)
Bone metastasis	12 (48%)
Brain metastasis	10 (40%)

Abbreviations: NSCLC = non–small-cell lung cancer; NOS = not otherwise specified; WHO = World Health Organization.

Patients and Methods

Patients

We identified patients with metastatic nonsquamous NSCLC who received pemetrexed for 12 months or more either as maintenance treatment after first-line platinum-based chemotherapy or as subsequent treatment at Stanford between October 1, 2007, and May 30, 2012, with the assistance of the Stanford Cancer Institute Research Database (SCIRDB) group. Stage was adjusted to conform to the 7th edition American Joint Committee on Cancer/International Union Against Cancer staging system (the 2009 tumor, node, metastasis classification system of malignant tumors).[14] Clinical and pathologic characteristics were collected using retrospective chart review. Adverse event (AE) information was retrospectively collected from the chart and classified according to the National Cancer Institute Common Terminology Criteria version, 3.0. Patients were defined as never-smokers if they had smoked ≤ 100 cigarettes in their lifetime. This chart review protocol was approved by the Stanford institutional review board.

Statistical Analyses

All statistical analyses were performed by SPSS software, version 19.0 (IBM, Armonk, NY). To select patients who had benefit from pemetrexed, the start date of pemetrexed was defined as the date of continuation or switch maintenance pemetrexed start (with or without bevacizumab) after completion of first-line platinum-based chemotherapy or from the initial administration date when given as a second-line or beyond treatment. PFS was taken as the interval from the date of pemetrexed initiation as maintenance therapy after first-line platinum-based chemotherapy or as a second-line or beyond treatment until first documented clinical or radiographic disease progression, disease escalation, or change in therapy (systemic progression), or death from any cause, as described in Camidge et al.[8] OS was measured from the date of pemetrexed initiation as