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A Case Series of Lengthy Progression-Free Survival With Pemetrexed-Containing Therapy in Metastatic Non–Small-Cell Lung Cancer Patients Harboring ROS1 Gene Rearrangements

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Introduction

c-ros oncogene 1 (ROS1), an orphan receptor tyrosine kinase, is a recently defined molecular subset of lung cancer identified in approximately 1% to 2% of screened patients.[1,2] Like anaplastic lymphoma receptor tyrosine kinase (ALK) translocations, ROS1 rearrangements lead to constitutive kinase activation and commonly arise in young nonsmokers with adenocarcinoma tumor histology.[3] Crizotinib (Pfizer), recently approved by the US Food and Drug Administration for treatment of metastatic non–small-cell lung cancer (NSCLC) patients with ALK rearranged tumors, has potent activity in cell lines with ROS1 translocations and recently demonstrated clinical activity in patients whose tumors harbor ROS1 rearrangements.[3,4]

Because of the recently discovered importance of ROS1 trans-locations in a small subset of NSCLC, we know little regarding the response to specific chemotherapeutics in patients whose tumors harbor these molecular alterations. Pemetrexed (Lilly) inhibits thymidylate

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synthase (TS) and other folate-dependent enzymes, and is a chemotherapeutic agent commonly used to treat nonsquamous NSCLC.[5]

Our institution conducted a retrospective case series of all meta-static lung cancer patients with ROS1 rearrangements. We recently began testing for ROS1 gene rearrangements using break-apart fluorescence in situ hybridization (FISH) in patients with lung adenocarcinoma and no other known mutations. A total of 129 ROS1 assays using FISH have been completed at Stanford with 5 ROS1 rearrangements identified; 1 additional patient treated at Stanford tested positive using FISH at an outside institution. Four of the 6 patients with detectable ROS1 rearrangements have metastatic cancer; and all 4 patients have a strikingly long progression-free survival (PFS) using pemetrexed—given as either single-agent second-line treatment or as part of front-line chemotherapy (Table 1).

Case 1

The patient is a 35-year-old never smoking woman who presented with dyspnea. Imaging revealed confluent pulmonary nodules in the left lung with a fluorine-18 fluorodeoxyglucose-avid pleural effusion. Mediastinoscopy showed N3 disease with right-sided mediastinal nodes positive for lung adenocarcinoma. The patient received 6 cycles of carboplatin, pemetrexed, and bevacizumab with a partial response followed by continuation maintenance with pemetrexed and bevacizumab for 21 cycles (Figure 1). During maintenance treatment, FISH was performed and revealed a ROS1 rearrangement. Bevacizumab was eventually discontinued because of nonspecific neurologic complaints. She continues on pemetrexed alone as maintenance therapy for > 14 cycles with minimal disease burden. Total time using pemetrexed is now > 36 months.

Case 2

The patient is a 64-year-old man with a distant light smoking history who presented with a palpable left supraclavicular lymph node. Biopsy of this node revealed lung adenocarcinoma. The patient's NSCLC was initially stage IIIB and he was treated with concurrent chemoradiation with carboplatin and paclitaxel. He developed biopsy-proven recurrence of disease 1 year later with multiple bilateral pulmonary nodules. He then received 6 cycles of carboplatin, pemetrexed, and bevacizumab with a partial response, followed by continuation maintenance pemetrexed and bevacizumab for 37 cycles. During maintenance treatment, a ROS1 rearrangement was detected by FISH. Proteinuria eventually led to discontinuation of bevacizumab. He continues taking pemetrexed alone as maintenance therapy for additional > 19 cycles. Total time taking pemetrexed is now > 47 months.

Case 3

The patient is a 56-year-old woman who presented with a chronic cough. Imaging revealed a large right hilar mass with multiple bone metastases, cervical, and mediastinal lymph nodes, and a frontal lobe brain lesion. Pathology obtained on endoscopic bronchial ultrasound showed lung adenocarcinoma. The patient received gamma-knife radiotherapy to her brain lesion. She then received 4 cycles of carboplatin and pemetrexed with treatment response

followed by pemetrexed continuation maintenance for 18 cycles. During maintenance treatment, ROS1 testing using FISH revealed a gene rearrangement. She developed progression of disease 18 months after starting pemetrexed with new liver lesions and bone metastases prompting initiation of crizotinib.

Case 4

The patient is a 65-year-old woman, never smoker, who presented with back pain. Imaging revealed multiple spinal metastases, brain metastases, a left lower lobe lung lesion, right adrenal metastasis, and extensive lymph node disease above and below the diaphragm. Bone biopsy showed lung adenocarcinoma. After receiving whole brain radiotherapy and palliative radiation to the spine, the patient received 4 cycles of carboplatin and paclitaxel with subsequent progression of disease. She then had an excellent treatment response to second-line pemetrexed. ROS1 testing using break-apart FISH performed during pemetrexed maintenance was positive (Figure 2). After 24 cycles of pemetrexed, therapy was stopped because of symptomatic pleural effusions and neurologic complications from radiation-induced accelerated dementia. She eventually deteriorated from neurocognitive complications of therapy and died without evidence of disease progression 24 months after starting pemetrexed.

Discussion

In our small case series, all 4 metastatic NSCLC patients who received pemetrexed (either as a single agent or in combination) and tested positive for a ROS1 rearrangement had prolonged PFS with pemetrexed. No patient received crizotinib before pemetrexed and only 1 patient needed to start crizotinib for subsequent disease progression. In the 2 patients who received pemetrexed/bevacizumab maintenance therapy, both patients continue to have clinical benefit to maintenance pemetrexed—even after discontinuation of bevacizumab because of side effects.

Three of the 4 patients with ROS1 rearrangements received pemetrexed as part of their front-line therapy and time on pemetrexed was > 36, > 47, and 18 months. In the phase III PARAMOUNT study, the median PFS for continuation maintenance pemetrexed after 4 cycles of cisplatin and pemetrexed was only 4.1 months.[6]

Our patient with a ROS1 rearrangement treated with pemetrexed in the second-line setting had a PFS of 24 months and eventually passed away from complications of treatment and not disease progression. By comparison, in previously treated patients, the median PFS of patients taking pemetrexed was 2.9 months; although 46% of the patients in this trial had squamous histology—a known predictor for lack of benefit to pemetrexed.[7] Among patients with nonsquamous NSCLC, median PFS was 3.1 months.[8]

Low tumor TS levels have been hypothesized to predict chemo-sensitivity to pemetrexed, but this has not been conclusively shown. Emerging retrospective data suggest a longer PFS in patients treated with pemetrexed whose tumors harbor ALK rearrangements.[9,10] This PFS benefit might be because of lower TS levels in ALK-rearranged tumors.[11] Another larger retrospective analysis showed prolonged PFS to pemetrexed only in patients with ALK-

rearranged tumors treated with first-line pemetrexed/platinum combination, but similar PFS in previously treated patients in ALK-rearranged and ALK wild type tumors who received pemetrexed and had a never or light smoking history—suggesting that never or light smoking history might be a better prognostic indicator of clinical benefit to pemetrexed than ALK status.[12] All 4 of our patients with ROS1 rearrangements were never or light smokers.

Conclusion

Our case series suggests that patients whose tumors harbor ROS1 rearrangements might preferentially benefit from treatment incorporating pemetrexed, though it is limited by its: retrospective nature, selection bias, and small sample size. All patients with metastatic NSCLC with ROS1 rearrangements at our institution had a PFS far exceeding published data of patients with ALK rearrangements and in patients with a never or light smoking history treated with pemetrexed. Larger data sets and further exploration of potential mechanisms underlying this observed dramatic PFS benefit of pemetrexed in lung cancer patients with ROS1 rearrangements is warranted.

Acknowledgments

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Clinical Practice Points

- Tumors with c-ros oncogene 1 (ROS1) translocations are a newly discovered molecular subset of non esmall-cell lung cancer (NSCLC). Like anaplastic lymphoma receptor tyrosine kinase (ALK)-rearranged NSCLC, early phase clinical trials show a high response rate to crizotinib in these patients. Some retrospective studies suggest patients with ALK^+ tumors have a longer progression-free survival (PFS) to pemetrexed compared with other chemotherapeutics—though this is controversial. Little is known about whether patients with ROS1-rearranged tumors preferentially respond to specific chemotherapy drugs.
- This small, retrospective case series suggests that some NSCLC patients whose tumors harbor the ROS1 gene rearrangements might have a lengthy PFS using pemetrexed-containing therapy.
- In clinical practice, oncologists might want to consider pemetrexed-containing regimens when chemotherapy is indicated.

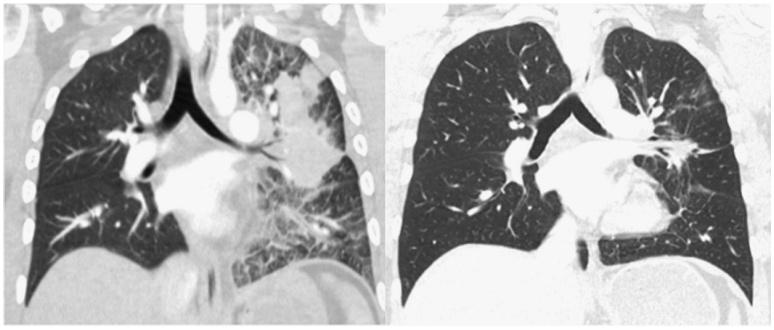

Figure 1.

Computed Tomography Scan of a NSCLC Patient With a ROS1 Gene Rearrangement Before Treatment (Left) and More Than 26 Months Later (Right) During Pemetrexed Continuation Maintenance

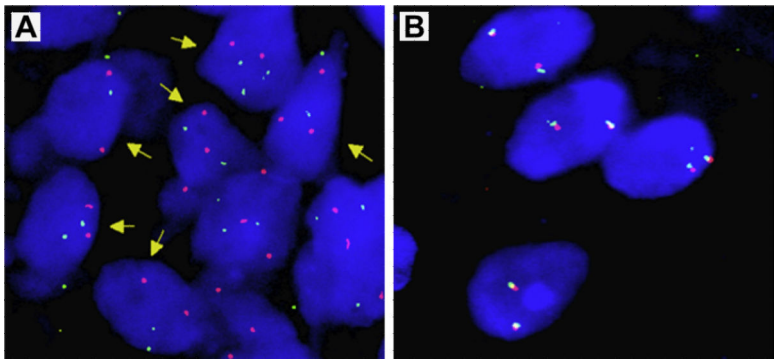

Figure 2.

Break-Apart ROS1 FISH of a NSCLC Patient (Case 3) Red Probes are Hybridized to the ROS1 3' Region and Green Probes Hybridized to the 5' Prime Region. ROS1-Positive Cells With Split Red and Green Signals (A) (Arrows) and Adjacent ROS1-Negative Cells (B) With Red-Green Colocalization

Table 1

Summary of ROS1 Cases

Case	Sex	Age, years	Treatment	PFS During Pemetrexed Treatment (mo)
1	F	35	CPB × 6 → PB × 21 → P × >14[a]	>36
2[b]	M	64	CPB × 6 → PB × 37 → P × >19[c]	>47
3	F	56	CP × 4 → P × 18 → crizotinib	18
4[d]	F	65	C-Pac × 4 → P × 24	24

Abbreviations: B = bevacizumab; C = carboplatin; F = female; M = male; P = pemetrexed; Pac = paclitaxel; PFS = progression-free survival.

[a] Bevacizumab discontinued because of nonspecific neurologic complaints.

[b] Case 2 initially stage IIIB at diagnosis and received concurrent chemoradiation with biopsy proven recurrence 1 year later.

[c] Bevacizumab discontinued because of proteinuria.

[d] Case 4 is the only patient who received pemetrexed as second-line treatment. She died from treatment-related complications, not progression.