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A Patient with Anaplastic Lymphoma Kinase (*ALK*) FISH Positive NSCLC with Development of Leptomeningeal Carcinomatosis while on Targeted Treatment with Crizotinib

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Abstract

Leptomeningeal carcinomatosis (LM) is an infrequent, yet morbid and often fatal complication of non-small cell lung cancer (NSCLC). Management of LM is multimodal, often involving systemic chemotherapy, radiotherapy, and a variety of symptom management maneuvers to address elevated intracranial pressure, pain and mood changes that can accompany the disease. Increasingly it is recognized that tumors with actionable mutations in NSCLC, including epidermal growth factor receptor (*EGFR)* mutations and anaplastic lymphoma kinase (*ALK*) translocations, respond well to systemic therapy with tyrosine kinase inhibitors yet often progress in the central nervous system (CNS). Therefore, more information is needed regarding the natural history and optimal management of leptomeningeal disease in specific molecular subtypes of NSCLC. The case below summarizes our institution's management of a patient with ALK-positive NSCLC who developed leptomeningeal carcinomatosis while on targeted treatment with crizotinib (Xalkori) within the context of current NCCN guidelines and recently published studies.

Keywords

NSCLC; Targeted Therapy; Leptomeningeal Disease; ALK Translocation

Case

The patient is a 55 year-old Asian man with minimal smoking history (1 pack-year in the distant past), but a significant history of coronary artery disease with stent placement requiring maintenance with clopidogrel (Plavix) and aspirin. He presented with subacute cough, scant hemoptysis, worsening dyspnea on exertion and night sweats. Chest X-ray upon return from a trip to Asia revealed a right upper lobe lung mass. Physical exam revealed a palpable right supraclavicular lymph node. Fine need aspiration biopsy of the

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supraclavicular lymph node showed metastatic adenocarcinoma of lung primary (CK7+, CK20-, TTF1+). The patient's tumor was negative for both *KRAS* and an *EGFR* activating mutations. PET-CT showed the right upper lobe lung mass as well as bone, liver and multiple lymph node metastases. MRI of the brain was negative for intracranial disease.

He was initially treated with carboplatin and pemetrexed for 6 cycles followed by continuation maintenance pemetrexed for 17 cycles until systemic progression was noted on CT scan with development of a new thoracic spine bone lesion, as well as growth in lung, lymph node and liver lesions. MRI of the brain at that time revealed an asymptomatic 9 mm brain metastasis that was treated with stereotactic radiotherapy.

He was then treated with erlotinib for 2 cycles but developed rapid disease progression. The patient was then placed briefly on docetaxel, but mucositis and neutropenia were dose limiting. *ALK* fluorescent in situ hybridization (FISH) testing became commercially available at this time and the patient's tumor was positive for an *ALK* translocation by break-apart FISH analysis. Crizotinib was initiated at 250 mg orally twice daily. He had a rapid partial response and symptomatic improvement, working full-time and traveling. This continued for 10 months but he then developed headache, confusion, nausea and vomiting. A MRI of the brain revealed enhancement of the leptomeninges consistent with leptomeningeal carcinomatosis, progressive brain metastases and ventriculomegaly (Figure 1). An elevated opening pressure of 32 mm H_2O was noted on lumbar puncture and CSF cytology was positive for metastatic adenocarcinoma. The patient's headache, nausea and vomiting resolved shortly after lumbar puncture. He completed palliative whole brain radiation to 30 Gy and received a ventriculoperitoneal (VP) shunt for increased intracranial pressure. Over the next several weeks he had recurrence of neurologic symptoms, so he was transitioned to hospice care.

Discussion

The mainstay of first-line treatment in patients with metastatic non-small cell lung adenocarcinoma whose tumors do not harbor an *EGFR* activating mutation or an *ALK* translocation is platinum based doublet chemotherapy with or without the VEGF inhibitor bevacizumab. NCCN guidelines for NSCLC currently list docetaxel, paclitaxel, pemetrexed, vinorelbine, vinblastine, gemcitabine and etoposide as proven effective agents when combined with carboplatin or cisplatin. In patients with non-squamous histology, a first line pemetrexed-based platinum doublet is frequently employed, with or without bevacizumab, based on phase III data showing on overall survival benefit of cisplatin/pemetrexed compared with cisplatin/gemcitabine in first line treatment of metastatic non-squamous histology lung cancer patients[1]. Pemetrexed containing first line regimens are well tolerated by most patients and have a much lower incidence of alopecia, neuropathy, and cytopenias than many other regimens. However, the additional benefit of adding bevacizumab to a platinum/pemetrexed backbone has been called into question by the recently presented Point Break Trial, which showed that overall survival was not increased with carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance compared to carboplatin/paclitaxel and bevacizumab followed by bevacizumab maintenance[2]. These

results have lowered enthusiasm for a pemetrexed backbone when bevacizumab is utilized, though this is still a reasonable first-line treatment regimen.

Several retrospective analyses have shown a progression-free survival (PFS) benefit with pemetrexed compared to other chemotherapy agents in patients with *ALK*+ tumors, although prospective data is lacking[3,4]. This benefit may be due to lower levels of thymidylate synthase (TS) seen in *ALK*+ NSCLC tumors[5]. However, recently published data indicates that the preferential activity of pemetrexed may be associated with patients who have a never or light smoker history rather than the presence of an *ALK* translocation, which in itself is also associated with a light/never smoking history[6]. In the absence of significant toxicity or progression, we often continue pemetrexed after 4–6 cycles of platinum/pemetrexed doublet chemotherapy, which is presently a NCCN Category 2A recommendation. A statistically significant 2.9 month median improvement in overall survival (OS) following continuation maintenance with pemetrexed was observed in the phase III PARAMOUNT trial, as presented at the 2012 ASCO Annual Meeting[7].

FDA approval of bevacizumab in NSCLC is based on the phase III ECOG 4599 clinical trial, in which the addition of bevacizumab to a carboplatin and paclitaxel backbone led to a statistically significant 2-month improvement in median overall survival in patients with non-squamous NSCLC[8]. One of the trial exclusion criteria was anti-coagulation, including patients with regular use of 325 mg of ASA or other inhibitors of platelet function. There is also a modest increased risk of coronary thrombosis in patients on bevacizumab[9]. In another large phase III randomized trial adding bevacizumab to cisplatin and gemcitabine, patients were allowed to stay on bevacizumab after occurrence of venous thrombosis on trial. In total, 9% of patients on this study were on anticoagulation with low molecular weight heparin or warfarin and none experienced pulmonary hemorrhage[10]. In a large phase IV trial including bevacizumab, the incidence of grade 3 or greater bleeding on anti-coagulation was 4%[11]. Several ongoing cooperative group clinical trials with bevacizumab and current NCCN guidelines do not prohibit patients on anticoagulation from receiving bevacizumab.

Though this patient had only scant hemoptysis, he had active coronary artery disease (CAD) with two recent stent placements and was on ASA 325 mg and clopidogrel, so the decision was made to withhold bevacizumab. Our institution is comfortable treating patients with anti-coagulation and bevacizumab based on the aforementioned data, but there remains concern in the setting of hemoptysis, active CAD or other arterial thrombotic disease and with clopidogrel and other very potent direct platelet inhibitors (ticlopidine, cilostazol).

Crizotinib (Xalkori), an oral ALK and MET small molecule tyrosine kinase inhibitor, has recently been given accelerated approval by the FDA for metastatic NSCLC patients harboring an ALK translocation as established by the companion FISH diagnostic test. Approval is expected based on the recently presented results of the phase III PROFILE 1007 (A Phase III Trial of Crizotinib Versus Standard of Care in Patients With Advanced Non–Small-Cell Lung Cancer With a Specific Alteration of the Anaplastic Lymphoma Kinase Gene) trial of crizotinib versus physician's choice of pemetrexed or docetaxel in the second-line setting and beyond. A PFS benefit (7.7 vs. 3 months) of crizotinib was noted, though no

OS benefit was seen in an interim analysis most likely due to the high degree of crossover (62%)[12].

FDA approval of crizotinib did not restrict its indication to the relapsed/refractory setting, so crizotinib can be given in the first-line even though the clinical trials presented to date have looked at it in patients who have progressed after first line chemotherapy. The current NCCN guidelines list crizotinib as a default category 2A recommendation, rather than conventional platinum based chemotherapy regimens, as first line therapy in metastatic NSCLC patients with FISH ALK+ tumors. The use of first-line crizotinib compared to cytotoxic chemotherapy is based on extrapolated data from the results of several large, randomized phase III trials showing improvement in progression-free survival, but not overall survival with EGFR targeted TKIs compared to platinum doublet chemotherapy in patients with tumors harboring EGFR activating mutations[13–15]. A randomized, phase III trial investigating first line crizotinib versus carboplatin or cisplatin and pemetrexed in patients with FISH ALK+ tumors is ongoing (NCT01639001).

This patient was diagnosed and started on first line chemotherapy before ALK FISH testing was routinely available. He developed leptomeningeal disease while on crizotinib. The CNS is a known site of progression with this agent[16]. In patients with ALK+ tumors who have active CNS disease we consider a pemetrexed-based regimen, preferably with platinum in a patient who is not heavily pretreated, and bevacizumab if they do not otherwise have a contraindication, as p pemetrexed appears to have activity in CNS disease[17,18]. Though bevacizumab administration is contraindicated in untreated parenchymal brain metastases, there is sufficient evidence at this time to support its use in patients with treated stable CNS disease[19,20]. There is also phase III data to support the use of bevacizumab in patients who develop radiation necrosis after brain irradiation for metastases[21]. We have given bevacizumab in patients with active leptomeningeal disease with some success and without significant toxicity, but it is not clear what role bevacizumab will ultimately play in the treatment of LM.

The mean cerebrospinal fluid (CSF) penetration of erlotinib is about 5–10% of the systemic concentration [22]. Pulsed high-dose erlotinib has been used as a strategy to treat LM in patients with tumors harboring EGFR activating mutations[23,24]. Crizotinib has some documented CSF penetration, though lower penetration compared to erlotinib[17]. However, leptomeningeal involvement of cancer may lead to compromise of the blood brain barrier with potentially increased CNS penetration. In a recent phase II study of crizotinib in patients with ALK+ tumors, 22% of patients with asymptomatic, non-irradiated brain metastases had a radiographic brain response[25].

After diagnosis of leptomeningeal disease, this patient received whole brain radiotherapy to 30 Gy and VP shunt placement with limited improvement in neurologic function. Analysis of LM outcomes is mainly from retrospective studies as prospective trials are limited for this uncommon complication. As in other malignancies, LM disease is a poor prognostic indicator in NSCLC[26]. Though whole brain radiotherapy has not shown an overall survival benefit in a retrospective analysis, we consider palliative brain and possibly spinal radiation in our LM patients for symptomatic relief[26]. If a patient with an ALK+ tumor develops

isolated CNS or other metastases while on crizotinib, radiating the site of progression and restarting crizotinib may delay further progression based on a retrospective analysis[16]. However, patients with LM disease were excluded from this analysis. There is no published data yet regarding the safety and efficacy of concurrent crizotinib and radiotherapy. Novel ALK inhibitors with potentially better CNS penetration are in development and will hopefully provide additional therapeutic options for patients like the one described here[27].

In a patient with hydrocephalus and symptomatic improvement following large volume lumbar puncture, as in this patient, we consider a VP shunt for palliative relief. Intrathecal chemotherapy with methotrexate or cytarabine or liposomal cytarabine or topotecan is also a treatment option that we use infrequently. A recent single institution, retrospective case-series noted prolonged survival in the small number of patients who received intrathecal chemotherapy, but this may be due to selection bias[26].

Leptomeningeal disease in NSCLC, as in other malignancies remains challenging to treat. However, some limited evidence is mounting that outcomes may be improved in the modern treatment era, though many of the studies are retrospective and thus limited by multiple biases[28]. A recent retrospective review at our institution also supports improved outcomes with modern systemic chemotherapy and targeted therapies, particularly in patients diagnosed with LM at metastatic presentation and who are typically naïve to systemic treatment[29]. Patients with NSCLC are living longer and we often seen CNS progression in patients with EGFR+ and ALK+ tumors after progression on targeted therapy that is difficult to treat. Whether this is a feature of the disease itself or the consequence of better systemic therapies and longer life is unclear.

Many patients with leptomeningeal disease have severe neurologic complications and poor functional status. Default category 2A NCCN recommendations for NSCLC patient with an ALK+ tumor and poor functional status (ECOG performance status of 3–4) post crizotinib and other first line chemotherapy treatments include best supportive care. Effective pain control as well as integrated palliative care is always critical in patients with leptomeningeal carcinomatosis who have progressed despite multiple lines of therapy. Hopefully, more effective targeted therapies, including ALK inhibitors with increased CNS activity, will be more successful in treating this devastating complication of NSCLC.

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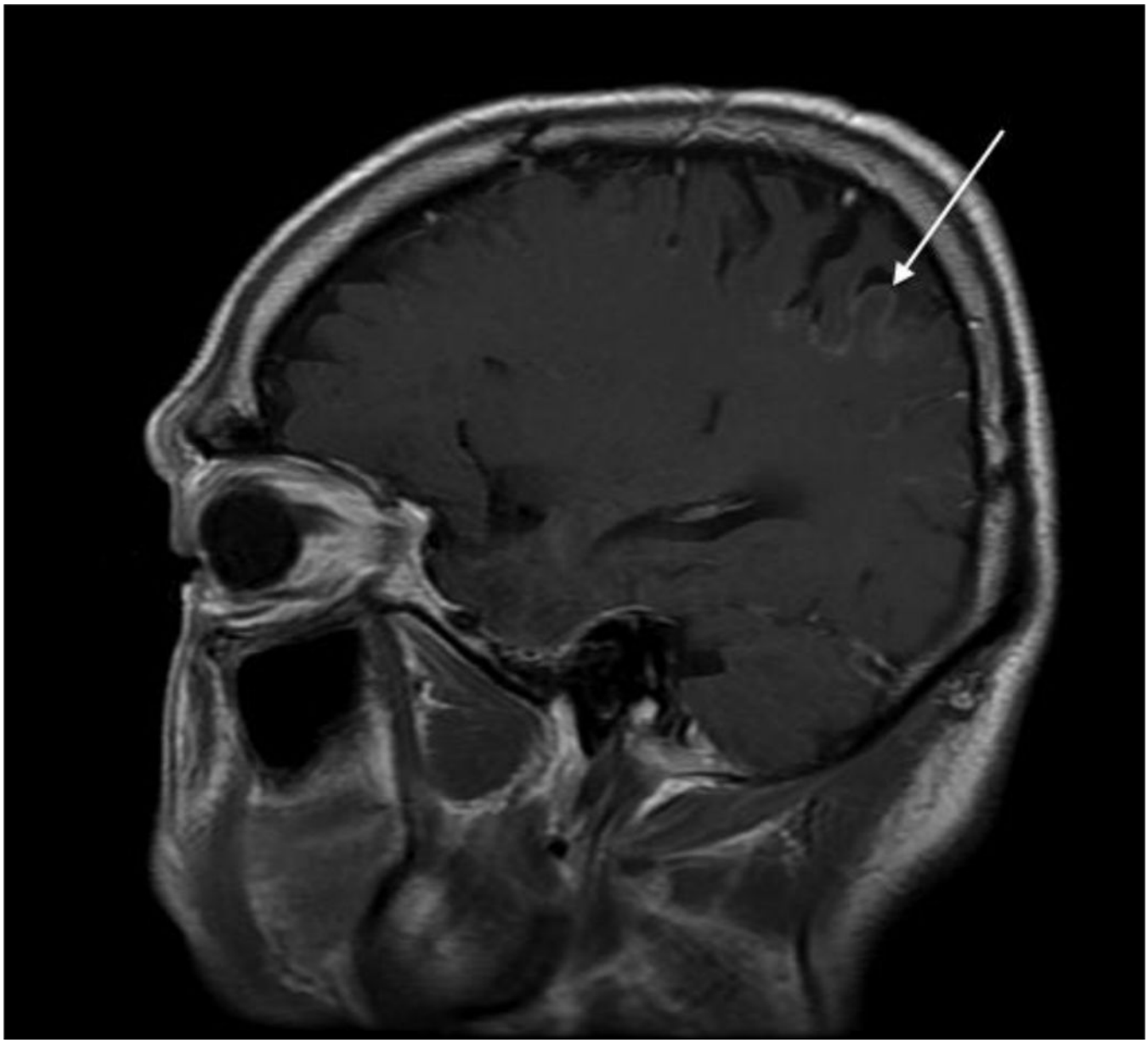

Figure 1:
The patient's MRI with gadolinium contrast showing abnormal enhancement of a cortical gyrus consistent with leptomeningeal disease (arrow).