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Clinical Study

Durable brain response with pulse-dose crizotinib and ceritinib in ALK-positive non-small cell lung cancer compared with brain radiotherapy

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ABSTRACT

Crizotinib achieves excellent systemic control in anaplastic lymphoma kinase-rearranged (*ALK+*) non-small cell lung cancer (NSCLC); however, central nervous system (CNS) metastases frequently occur as an early event. Whole brain irradiation, the standard treatment, results in neurocognitive impairment. We present a case series of three *ALK+* NSCLC patients with progressing CNS metastases who were treated with pulse-dose crizotinib followed by ceritinib. Three *ALK+* NSCLC patients treated between 2011 and 2014 (two males, two never smokers, age range 20–54 years, all echinoderm microtubule-associated protein-like 4/*ALK* rearrangement), were diagnosed with progressing cerebral disease while receiving crizotinib. Clinico-pathological characteristics, treatments, and outcomes were analyzed. In two patients the progression was limited to the CNS, and radiological evidence of leptomeningeal spread was present in one patient. Sequential use of crizotinib 500 mg administered once daily (pulse-dose) followed by ceritinib on progression achieved control of the disease in the CNS for over 18 months and over 7 months in Patient 1 and Patient 2, respectively. This strategy provided durable CNS control after whole-brain radiotherapy failure in Patient 1, and allowed the whole-brain radiotherapy to be deferred in Patient 2. Limited CNS progression was documented in Patient 3 while he was on standard-dose/pulse-dose crizotinib for 15 months; durable (over 7 months) complete remission was achieved with stereotactic radiotherapy and ceritinib. Manipulating the crizotinib schedule in *ALK+* NSCLC patients with CNS metastases and using a novel *ALK*-inhibitor at the time of further progression may provide durable CNS control and allow brain radiotherapy to be deferred.

1. Introduction

Chromosomal rearrangements involving the anaplastic lymphoma kinase *(ALK)* gene occur in 3–5% of non-small cell lung cancer (NSCLC) patients [1]. Anaplastic lymphoma kinase-rearranged *(ALK+)*-tumors demonstrate marked sensitivity to *ALK*-tyrosine kinase inhibitors (TKI), such as crizotinib (Pfizer, New York, NY, USA), ceritinib (Novartis, AG, Basel, Switzerland), alectinib (Chugai-Roche, Basel, Switzerland), AP26113, and X-396 [1–5]. Activity of crizotinib in the first-line setting has been extensively evaluated, with 60–75% of patients achieving an objective response and a progression-free survival of about 10–11 months [1,6]. Currently, crizotinib comprises the only first-line therapy approved by the USA Food and Drug Administration for this subset of patients.

The central nervous system (CNS) is the primary site of initial treatment failure in about 50% of crizotinib-treated *ALK+* non-small cell lung cancer (NSCLC) patients [1,7]. Intracranial progression is an early event which occurs within 7 months of starting treatment [8]. Frequently, it also comprises the only site of disease progression [9]. Extremely low cerebrospinal fluid (CSF)-to-plasma ratio of only 0.0026 has been reported for crizotinib prescribed at a

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standard dose [10], and this pharmacokinetic phenomenon seems to be the main reason for the impaired control of the disease in the CNS.

Whole brain irradiation (WBRT) is administered to the vast majority of patients whose disease progresses in the brain, which frequently results in long-term cognitive decline [11]. Systemic strategies lacking long-term morbidity could be an effective alternative, and these are rapidly evolving [3–5,12–14]. We present a series of cases that questions the timing and possibly the role of radiotherapy in the management of brain metastasis in *ALK*+ tumors.

2. Materials and methods

Three patients treated at Davidoff Cancer Center and Sheba Medical Center, Israel, between July 2011 and October 2014 were diagnosed with an *ALK*+ adenocarcinoma of lung and progressing cerebral metastases while receiving crizotinib. Clinicopathological characteristics, treatments, and outcomes were analyzed.

3. Results

3.1. Illustrative Patient 1

A 47-year-old never-smoking man who was previously reported in the *Journal of Thoracic Oncology* [12,15] is presented here again due to his dramatic response of brain metastases to ceritinib. Two previous reports were on a complex immunohistochemistry-positive, fluorescent *in situ* hybridization-negative *ALK* rearrangement in this patient's tumor and on the response of brain metastases to pulse-dose crizotinib after failure of both conventional-dose crizotinib and WBRT.

The patient continued on crizotinib 500 mg administered once daily, and tolerated treatment extremely well. After a follow-up of 11 months, he presented with confusion and general seizures. Blood work-up revealed no significant electrolyte abnormalities. MRI of the brain demonstrated diffuse worsening of the known intra-parenchymal lesions and appearance of new lesions compatible with leptomeningeal spread (Fig. 1). Positron emission tomography CT (PET-CT) scanning showed no evidence of active systemic disease.

At this point, therapy with ceritinib 750 mg daily and antiepileptic therapy with valproic acid was initiated. A month later, the dose of ceritinib was reduced to 450 mg/day because of grade 3 diarrhea. Two months later even further dose reduction was required because of anorexia, and the patient continued on ceritinib administered daily at 450 mg or 350 mg on alternate days. Follow-up brain MRI was performed 4 months after the initiation of treatment, and revealed marked reduction in the multiple intra-parenchymal and leptomeningeal CNS metastases (Fig. 1). Repeat brain MRI 3 months later demonstrated further stabilization of cerebral disease (images not shown). At the time of writing the patient continued to have overall stable intracranial disease without active systemic disease 7 months after the initiation of therapy. Moderate radiation-induced memory decline, mood and concentration impairment were notable though.

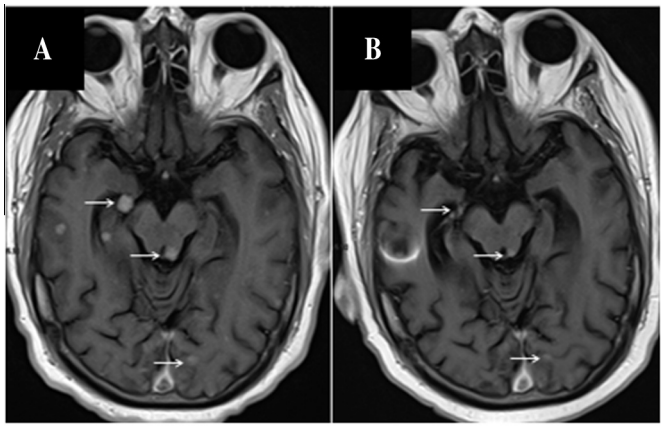

Fig. 1. Regression of central nervous system metastases on ceritinib therapy (Patient 1). Contrast-enhanced axial T1-weighted MRI in a patient with brain parenchymal and leptomeningeal metastases (arrows) before (A) and 4 months after (B) the initiation of therapy.

3.2. Illustrative Patient 2

A 19-year-old never-smoking woman was diagnosed with adenocarcinoma of lung, stage IIIA (pT1bN2M0). At the time of the initial diagnosis, the patient underwent right lower lobe lobectomy and mediastinal lymph node dissection followed by adjuvant chemotherapy with cisplatin/pemetrexed and post-operative chest radiotherapy. Molecular analysis of her tumor revealed the presence of an (echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* rearrangement. She was subsequently found to have an asymptomatic CNS recurrence in the form of multiple brain metastases. Therapy with crizotinib 250 mg twice daily was initiated, and resulted in excellent CNS control for 6 months.

However, asymptomatic cerebral disease progression, mainly in the form of small brain metastases, was documented on a brain MRI performed 6 months later (Fig. 2). At that point, crizotinib therapy was modified to a single daily administration of 500 mg. After 2 months of therapy, a repeat brain MRI scan demonstrated stabilization of intracranial disease (images not shown). However, subsequent imaging performed 2 months later showed minimal growth of cerebral metastases (Fig. 2). The patient remained free of neurological symptoms. She only suffered from mild leg edema which was successfully managed with furosemide 40 mg daily.

Treatment was switched to ceritinib 750 mg daily when the drug became commercially available. One month later, the patient developed progressive dyspnea and chest pain, and was diagnosed with a large cytology-negative pericardial effusion which was attributed to the side effects of treatment. After the fluid evacuation, colchicine 0.5 mg/day and prednisone 40 mg/day were started, and ceritinib dose was reduced to 350 mg daily. Later, even further dose reduction was required because of grade 3 rash. Repeat brain MRI performed 1.5 months after the ceritinib initiation demonstrated dramatic improvement in all the intracranial metastases despite the dose adjustments which have been performed (Fig. 2). A follow-up examination was done a month later, and showed minimal enhancement of the known cerebral lesions, while the patient remained free of neurological symptoms. Notably, technical differences (1.5 *versus* 3.0 Tesla machine, differences in slice thickness and slice angulation) probably accounted for the slight changes in the imaging findings (Fig. 2). It is also remarkable that PET-CT imaging demonstrated no evidence of systemic recurrence through the entire disease course.

At the time of writing, the patient had only minimal rash, and imaging studies were negative for recurrent pericardial fluid. She remains progression-free on therapy 3 months after the ceritinib initiation.

3.3. Illustrative Patient 3

A 54-year-old smoking man presented with hemoptysis, lower back pain and weight loss. PET-CT scan demonstrated a left upper lobe mass, mediastinal lymphadenopathy, and multiple lytic bone