Case Report

# NOVEL TREATMENT FOR NON-SMALL CELL LUNG CANCER WITH BRAIN METASTASES

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**ABSTRACT**

*Brain metastasis is common in patients with non-small cell lung cancer (NSCLC) and it is associated with poorer prognosis. Several options to control the secondary brain tumors in the context include chemotherapy, whole-brain radiation, stereotactic surgery, surgery. However, chemotherapy is ineffective to those patients because of poor penetration through the blood-brain barrier. Whole-brain radiation therapy used to be a standard option for brain metastases. However, it potentially damages normal brain tissues and causes neurocognitive decline. Stereotactic radiotherapy has been considered in cases of three or fewer lesions, and the lesions less than 3 cm. In selective cases, surgical removal of brain metastases can be done. These local therapies were accompanied by systemic treatment due to spreading of the cancer. Recently, molecular targeted therapy has opened up a new era in cancer treatment, especially NSCLC with brain metastases. In this review, we discuss brain metastases occurring in NSCLC patients with driver gene mutations with some briefly demonstrated cases.*

## I. INTRODUCTION

In 2018, lung cancer occurred in approximately 2.1 million patients, and there were about 1.7 million deaths all over the world. [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers.[2] Although there have been many advances in early detection and standard treatment, NSCLC is often diagnosed at an advanced stage because of its hard-detected symptoms. By that time, the prognosis usually remains poor. Advanced NSCLC often progresses to brain metastases with the incidence at about 16 to 20 percent of all cases. However, there were evidences suggesting that certain molecular subtypes have an increased propensity for the development of brain metastases, including those with an epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement. The incidence to develop brain metastasis can be up to 50 to 60 percent among these patients [3][4][5][6]. Of all newly diagnosed patients with advanced NSCLC, approximately 10 percent of patients presented with

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brain metastases[3]. In addition, a further 25-40% of all NSCLC patients will develop brain metastasis during the course of their disease.[7]

In the past, chemotherapy was the primary treatment for those at advanced stages. However, the treatment outcomes were limited because almost chemicals could not or less pass through the blood-brain barrier [8][9]. Many patients were just treated with symptomatic medication to control symptoms such as cerebral oedema, convulsion... Median survival for those patients was only 1 month from diagnosis in the absence of treatment, 2 months with glucocorticoid therapy[10][11][12][13][14][15], and about 2.4-4.8 months when given whole-brain radiation therapy.[10]

In the early 2000s, the improvement in understanding of the molecular pathways that drives malignancy in NSCLC, as well as other neoplasms, led to the development of agents that target specific molecular pathways in malignant cells. It has opened up a new era in the treatment of various forms of cancer from traditional chemotherapeutics to targeted therapy.

Molecular targeted therapy refers to the use of drugs or other substances to target specific molecules involved in the growth and the spread of maglinant cells. The concept for targeted therapy began from the idea of “magic bullet” first expatiated by Paul Rich in late 1800 (Ehrlich, 1906). In the beginning, it was used to depict the ability of a chemical that targets microorganisms specifically, however; it has since been expanded to cancer treatment (Brodsky, 1988).[16]

It is necessary to identify gene mutations for selecting the right medication. Clinicians have to obtain a biopsy or plasma sample of patients to detect the mutation. The physician will subsequently choose the treatment method for lung cancer patient based on the mutation result.

EGFR (epidermal growth factor receptor) activating mutations are the most common, present in about 50% of Asian patients and 10-15% of white patients with NSCLC of adenocarcinoma. Those patients with adenocarcinomas, never-smokers or light smokers and are of Asian ancestry are prone to have EGFR mutation. [9] ALK (anaplastic lymphoma kinase) gene rearrangements are the second most common, which occur in 3-5% of NSCLC patients. Like EGFR mutant lung cancer, ALK rearrangements are more prevalent in never-smokers and light-smokers with adenocarcinoma [9]. Besides, there are several small-molecule tyrosine kinase inhibitors (TKIs) that have been found and show efficacy in targeting the associated pathways.

Patients with advanced EGFR-mutant or ALK-positive NSCLC have a high cumulative risk (>70%) for developing brain metastases during the course of their disease. However, there are many recent clinical studies established that many EGFR and ALK TKIs have a good penetration on the central nervous system (CNS), at times achieving CNS response rates between 40% and 70% in EGFR-mutant or ALK-positive NSCLC.[9]

Among EGFR TKIs, osimertinib was proved to have advanced the furthest in clinical development and is the only third-generation EGFR TKI that has obtained the FDA approval. Furthermore, the median central nervous system progression-free survival was also significantly longer with osimertinib than with chemotherapy (11.7 vs. 5.6 months; HR 0.32, 0.15, 0.69; p =0.004)[17]. Besides, it also has an improved toxicity profile in comparison with the first- and second-generation EGFR TKIs. Therefore, the authors of the FLAURA study came to the conclusion that osimertinib should be considered the new standard of care as first-line treatment

for patients with advanced NSCLC with EGFR sensitizing mutations, especially in those with brain metastasis.[18]

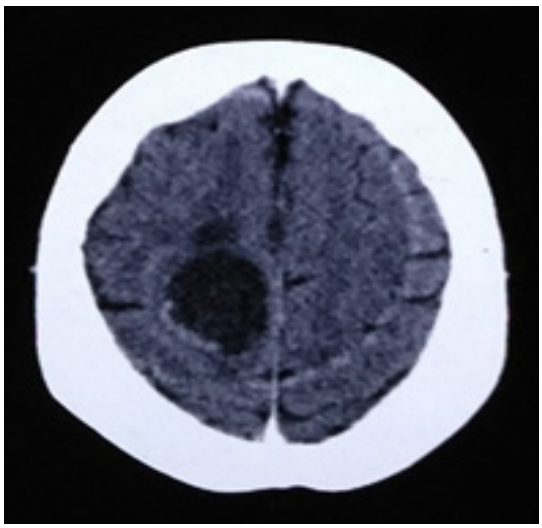
Asymptomatic brain metastases are particularly common in patients with ALK-positive NSCLC. All three principal ALK inhibitors have shown efficacy in treating brain metastases.[19] However, in Lancet Oncology published in 2018, Suresh Ramalingam (Emory University School of Medicine, Atlanta, GA, USA) stated that there was data showing high central nervous system responses and disease control with alectinib. Besides, he added: "Consequently, ALK-positive patients with asymptomatic brain metastasis can skip radiotherapy and be effectively treated with alectinib. This report provides further evidence to use alectinib as first-line therapy for metastatic ALK-positive NSCLC".[20]

**II. CLINICAL DEMONSTRATION OF TWO ADVANCED NSCLC PATIENTS WITH BRAIN METASTASES HAD WELL RESPONSES TO MOLECULAR TARGETED THERAPY**

Patient 1

A 68-year-old female patient was diagnosed with adenocarcinoma of the right lung stage IV (pleurae, liver and bone metastases) in 2016. Progression of the disease with brain metastasis after 2 regimens of chemotherapy. She was treated with Pemetrexed. The brain tumor progressed from 1.4cm to 6cm in diameter with serious headache and hemiparalysis with pemetrexed. Epidermal growth factor receptor exon 19 deletion was found. She was treated with EGFR TKI: Osimertinib. Her headache and hemiparalysis were improved and she could walk again.

CT scan images before and after Osimertinib



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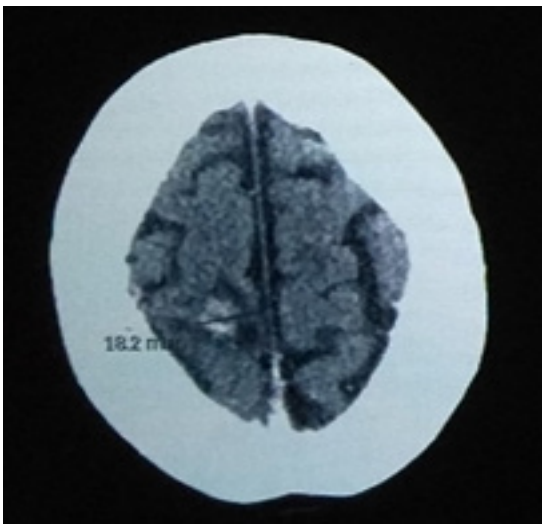
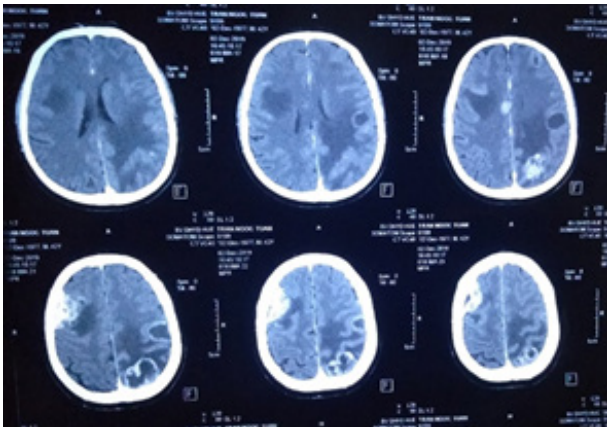


15 July, 2020

Patient 2

A 43-year-old male patient was diagnosed with NSCLC stage IV in 2017 (pleura and bone). He got a good response to chemotherapy at first. However, the disease got worse and the tumor spread to pleurae, bone, brain and meninges. He was admitted to the emergency with a large amount of pleural diffusion, serious headache, paralysis together with severe seizure. He was treated with Osimertinib. After 6 months, all of the neural symptoms improved, he had no seizure and could walk again.

CT scan images of the brain tumors before and after Osimertinib



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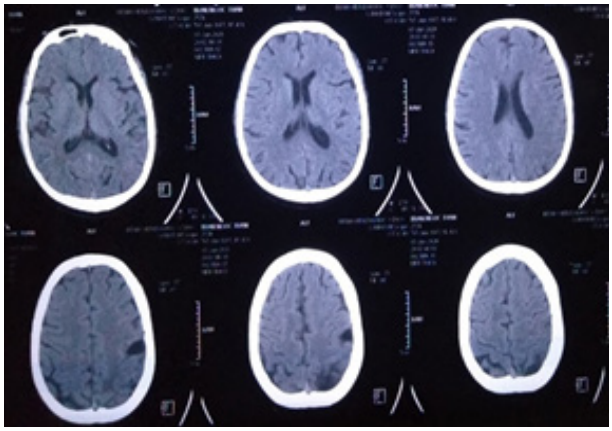

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## III. CONCLUSIONS

Targeted therapy has been found to be highly effective with brain tumors secondary to NSCLC with their ability to pass the blood-brain barier. Hence the role of local therapies for brain metastases in this population may be less important as in the past.

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