ALK and ROS1 Positive Non Small Cell Lung Cancers Are a Rare But Treatable Condition: A Case Report

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The National Cancer Registry reports that 7288 Irish people were diagnosed with lung cancer between 2013-2015. Lung cancer is not a single entity but a combination of different neoplastic diseases arising in lung tissue. It is divided between Small Cell with cells containing dense neurosecretory granules and Non-Small Cell Lung Cancer (NSCLC). The latter is subdivided into adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma. Adenocarcinoma of lung can be further described by the presence or absence of single druggable oncogenic driver mutations. Point mutations in the Epidermal Growth Factor Receptor are the commonest example accounting for 12% of European NSCLC. Anaplastic Lymphoma Kinase (ALK, 3-5%) and Proto-oncogene tyrosine-protein kinase ROS (ROS1 <2%) fusions are rarer. In ALK mutated lung cancer chromosomal rearrangements fuse the EML4 and ALK genes with the resulting oncogene coding for activated ALK proteins driving carcinogenesis. ROS 1 rearrangements are similar. In all cases a signaling molecule is permanently activated causing cell growth and division.

These types of lung cancer are treated with oral small molecule Tyrosine Kinase Inhibitors (TKI) which bind to the mutant protein preventing phosphorylation of tyrosine residues on downstream signaling proteins. Alectinib, a second generation TKI, is first line standard of care in Ireland. Second line treatment in Ireland is with the 3rd generation drugs Lorlatinib or Brigatanib. Alectinib does not bind to ROS1. The first generation TKI Crizotinib which is no longer used in ALK mutated cases is the first line treatment for ROS1 cases. The median overall survival for patients with Stage IV ALK mutated cancer is 6.8 years, when treated appropriately with TKI therapy, In ROS1 the two-year survival rate is 54%. These druggable mutations are very treatable but not curable. Therapeutic goals are maximizing progression free survival and improving quality of life. These cancers tend to be chemosensitive but cytotoxic platinum and pemetrexed based therapy is held in reserve until all targeted options have been exhausted.

Patients with druggable mutations tend to be young, female, life long non-smokers of Asian ancestry. Ideally all Stage IV adenocarcinoma of lung should have next generation sequencing to exclude treatable mutations but at a minimum EGFR and ALK should be tested for.

CASE REPORT

In 2017 a previously very fit and well Caucasian 45-year-old lady presented to the Bon Secours Hospital with painless obstructive jaundice and back pain. CT TAP demonstrated a large spiculated lung mass with massive mediastinal lymphadenopathy, hepatomegaly and hypodense lesions in the spine. She also had multiple small (<6mm) asymptomatic brain metastasis). The cancer was found to be ROS1 positive on FISH testing. A biliary stent was placed in situ to relieve her hepatic symptoms and she commenced on Zoledronic acid and Crizotinib. There was a good partial response initially. However, after 5 months she developed asymptomatic progression in her brain and liver. Lorlatinib is a potent, brain-penetrant, third-generation anaplastic lymphoma kinase (ALK)/ROS1 tyrosine kinase inhibitor which can cross the blood brain barrier. Lorlatinib was accessed under a compassionate access program as it is not licensed in ROS1.

The washout period between TKI is usually limited to 4-5 days. However, this patient was given a 10 day break off of Crizotinib in order to facilitate a Christmas holiday. On return from her holiday she had new headache and staggering gait. MRI brain demonstrated remarkable progression of her intracranial metastatic disease with her largest nodule now 12mm and more metastatic deposits evident on MRI. She commenced on Lorlatinib 100mg and within 4 months has demonstrated a phenomenal interval improvement in both her brain and liver. Her MRI brain showed a dramatic decrease in metastatic bulk and displayed very small foci of treated metastatic disease, largest 5mm, which decreased further and within 1 year disappeared entirely.

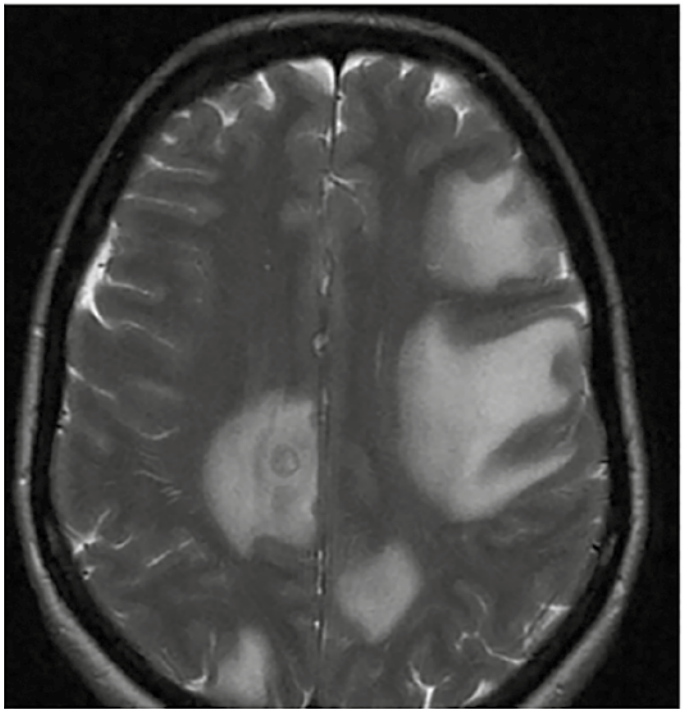
Over 80% of patients on Lorlatinib develop hypercholesterolemia and hypertriglyceridemia. Her cholesterol increased to over 8 from a normal baseline and she commenced Rosuvastatin with good effect. After 3 years, this patient remains in good health and enjoys good quality of life. She has had radiotherapy to an isolated site of disease progression in a pelvic lymph node. With other sites of slowly growing nodal disease emerging her case was discussed at a molecular tumour board. She has been referred to London for consideration of a phase 2 trial of the novel agent repotrectinib.

ALK/ROS1 INHIBITOR DISCUSSION

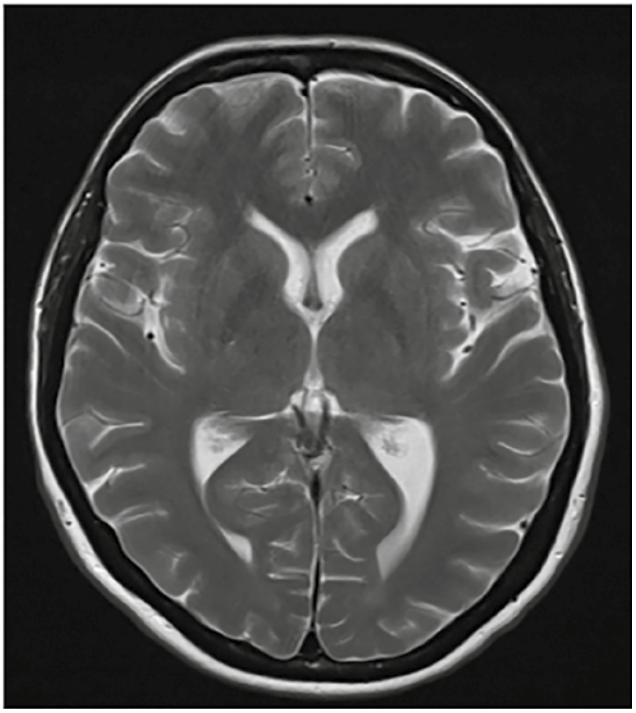
Patients with stage IV NSCLC can have a number of druggable mutations, including EGFR, ALK, ROS1, RAF, And HER2 among others. Patients with ALK or ROS1 mutations are treated with ALK/ROS1 Inhibitors. The ROS1 oncogene encodes an orphan receptor tyrosine kinase related to anaplastic lymphoma kinase (ALK), and is a member of the insulin-receptor family.

CRIZOTINIB

Crizotinib Is an ALK/ROS1 inhibitor that has been shown to provide benefit in patients with druggable gene mutations. The kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites. Crizotinib binds with high affinity to both ALK and ROS1, and is used as first line therapy in patients with ROS1 lung cancer in Ireland but has been superseded by Alectinib for ALK In the PROFILE 1014 trial compared Crizotinib to chemotherapy with a significant improvement in PFS in the Crizotinib arm [median, 10.9 vs. 7.0 months; hazard ratio (HR) for progression or death with Crizotinib =0.45; 95% confidence interval (CI): 0.35 to 0.60; P<0.001]. The objective response



MRI Brain off TKI DEC 2017



MRI Brain on Lorlatinib April 2018

rates were 74% for Crizotinib and 45% for chemotherapy (P<0.001), with disease control rates of 95% for the Crizotinib arm and 88% for the chemotherapy arm. In ROS1-positive NSCLC patients treated with Crizotinib showed an objective response rate of 54%. All patients eventually evolve resistance to TKI but not all patients are fit for a second line TKI or cytotoxic chemotherapy.

ALECTINIB

It is also noted that many patients with ALK-positive NSCLC will develop resistance to Crizotinib. This is due to secondary resistance mutations of the kinase encoding gene. A report of the pooled efficacy and safety data of two single-arm phase II studies of alectinib (NP28761 and NP28673) concluded that Alectinib demonstrates robust activity in crizotinib resistant patients, with a systemic objective response rate of 51% and a median progression free survival of 8.3 months.

Two randomized phase III studies which compared first line alectinib with crizotinib: J-ALEX conducted in Japan, and ALEX, conducted globally. The initial data from J-ALEX demonstrated superiority for alectinib compared with crizotinib in terms of progression free survival [HR: 0.34; 99.7% confidence interval (ci): 0.17 to 0.71; p < 0.001]. The median progression free survival was not reached (95% ci: 20.3 months to not estimable) in the alectinib arm; it was 10.2 months (95% ci: 8.2 months to 12.0 months) in the crizotinib arm. The ALEX study confirmed the superior efficacy and lower toxicity of alectinib compared with crizotinib in the primary treatment of ALK-positive NSCLC, with a Hazard ratio for disease progression or death of 0.47 (95% ci: 0.34 to 0.65); the independent review committee–assessed PFS also favoured alectinib, at 25.7 months (95% ci: 19.9 months to not estimable) compared with 10.4 months for crizotinib treatment (95% ci: 7.7 months to 14.6 months).

LORLATINIB

One treatment which proved very efficacious in both ROS1 and crizotinib resistant ALK positive NSCLC is Lorlatinib. Lorlatinib is a third-generation, oral, reversible, ATP competitive macrocyclic tyrosine kinase inhibitor of ALK and ROS1. It was designed to specifically penetrate the CNS in order to overcome secondary resistance mutations, It has been evaluated in Phase III CROWN study and demonstrated its efficacy over crizotinib in ALK positive NSCLC with a significant increase in Progression free survival over crizotinib. Progression free survival was 18.3 months (95% CI 16.4, 20.1) for lorlatinib and 14.8 months (95% CI 12.8, 18.4) for crizotinib in a sample size of 149 patients.

Due to its lipophilic nature Lorlatinib can easily cross the blood brain barrier and functions very effectively on intracranial disease in ROS1 Mutations. A Pfizer funded single arm phase II trial published in the Lancet, shows that Lorlatinib had clinical effect on both TKI naive patients and Crizotinib resistant patients particularly in brain metastasis Intracranial responses were achieved in seven (64%; 95% CI 31–89) of 11 TKI-naive patients and 12 (50%; 29–71) of 24 previous crizotinib-only patients.

However as Illustrated in the CROWN III study and demonstrated by the preceding case report. Lorlatinib is associated with a number of side effects that must be managed. It is most commonly associated with high blood cholesterol and high triglycerides. Patients with Atrioventricular block or a prolonged PR interval must also be excluded from therapy unless previously paced as Lorlatinib is associated with worsened AV Block and the use of a strong CYP3A4/5 inducer is contraindicated (e.g. rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) as they may decrease plasma concentrations of Lorlatinib.

REPOTRECTINIB

Repotrectinib is a potent ATP-competitive inhibitor against ALK, ROS1, TRKA, TRKB and TRKC recombinant kinases. In laboratory studies Repotrectinib potently inhibited in vitro and in vivo tumor growth and ROS1 downstream signal in treatment-naïve tumour xenografted cells (found in mice) compared with clinically available crizotinib, ceritinib, and entrectinib. Repotrectinib also possessed the strongest anti tumour suppression post drug withdrawal compared with Lorlatinib with tumours in 75% of mice examined remaining suppressed for over 80 Days post drug withdrawal, while 50% of Lorlatinib treated mice regrew tumours in 10 days. Repotrectinib also demonstrates potent intracranial activity comparable to lorlatinib as well as sharing the ability to overcome crizotinib resistant disease. In the phase 2 TRIDENT-1 study 5 of 10 pre-treated patients with ROS1-positive NSCLC had stable disease. It appears repotrectinib represents an exciting new step in the journey of managing metastatic ROS1 NSCLC, however more studies are needed to establish a safety profile and mechanisms of resistance to therapy.

CONCLUSIONS

In Ireland, ALK and ROS1 positive non small cell lung cancer patients are uncommon. Thankfully, the use of tyrosine kinase inhibitors has paved the way for impressive progression free survival and improved quality of life overall by relieving symptomatic burden and allowing patients a greater amount of time to spend with their families. The latter statement rings especially true when one considers that the majority of ALK/ROS1 patients are reasonably young, never smokers, as illustrated by the case report. However, by availing of these novel therapies we can continue to maximize the quality of life and progression free survival of those that are diagnosed.

References on Request