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CASE REPORT

Incretin Receptor Agonist, Semaglutide, as a Treatment for Alectinib-Induced Excessive Weight Gain. A Case Report

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Abstract: Alectinib is a second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) that has been widely used as first-line (1L) treatment of advanced *ALK*+ non-small cell lung cancer (NSCLC) ever since its approved indication on November 17, 2017, based on the ALEX trial and its perceived well-tolerability. Lorlatinib, a third-generation ALK TKI, achieved 1L indication on March 3, 2021, but is generally associated with adverse events including weight gain in up to 44% of patients from the recent update of the CROWN study; hence its use as 1L treatment has lagged behind alectinib. Recently, alectinib has also been reported to cause significant weight gain. Incretin receptor agonists such as glucagon-like peptide-1 receptor (GLP-1) agonists semaglutide have been approved to treat obesity (body mass index [BMI] ≥ 30). Here, we report a patient's case who had gained significant weight during still on-going 12-year treatment with alectinib and achieved weight loss through semaglutide but discontinued several months after starting semaglutide due to acute gallstone pancreatitis requiring emergency cholecystectomy. We believe this is the first case report on the efficacy and potential adverse events of GLP-1 agonist in treating the weight gain induced by alectinib.

Keywords: alectinib, weight gain, semaglutide, obesity, GLP1 agonists

Introduction

Alectinib, a widely used second-generation anaplastic lymphoma kinase tyrosine kinase inhibitor as first-line treatment of advanced *ALK*+ non-small cell lung cancer (NSCLC) based on the ALEX trial based on its efficacy and perceived tolerability.[1] Recently, excessive weight gain, especially increase in waist circumference and abdominal obesity, leading to metabolic syndrome in select patients, has been reported in patients receiving alectinib, although this had not been previously reported to be associated with alectinib.[2,3] Lorlatinib, a third-generation ALK TKI, is associated with weight gain as part of its spectrum of adverse events. From the 5-year update from the CROWN study, weight gain occurred in 44% of lorlatinib treated patients with 23% of the treated patients having ≥ grade 3 weight gain (between 10% and 20% increase from baseline).[4] There are two widely utilized incretin receptor agonists, semaglutide, a mono-GLP-1 agonist and tirzepatide, a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist.[5,6] However, the efficacy and toxicities of these GLP-1 agonists in managing weight gain induced by ALK TKIs have been limited and incomplete at best.[7,8]

In this case report, we describe a young *ALK*+ NSCLC patient who developed significant weight gain during the later part of her on-going 12-year treatment with alectinib first started in 2013 during the phase 1 US trial of alectinib, who developed weight gain which was successfully treated with semaglutide but had to stop due to gallstone pancreatitis and subsequent cholecystectomy.

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Case Presentation

Our patient is currently a 40-year-old female never-smoker who was diagnosed with locally advanced *ALK*+ NSCLC at age 22. She underwent surgical resection, adjuvant chemotherapy and enrolled onto crizotinib clinical trial at relapse. Upon progression from crizotinib, she received alectinib at 750 mg twice daily in August 2013 as a single patient investigational new drug (IND) application due to ineligibility for the US phase 1–2 alectinib trial from lack of measurable disease and presence of leptomeningeal carcinoma. Alectinib 750 mg twice daily induced an on-going durable complete response of >15 months in her leptomeningeal carcinoma at the time of our report.[9] At the time of starting alectinib in August 2013, the patient's weight was 57.0 kg. Within the first month, she experienced a 7 kg weight gain from tumor responding to alectinib, but her weight subsequently stabilized between 61 and 62 kg for several years. Her weight steadily increased after seven years of alectinib, with her weight peaking at 78.4 kg in October 2022, representing a 36.8% weight gain from her baseline weight (Figure 1). In May 2023, by her primary care physician, she was started on semaglutide with 0.25 mg weekly injection with monthly step up, and she subsequently lost approximately 8 kg over a one-month period (75.6 kg to 67.6 kg). Semaglutide was increased to 0.5 mg weekly in July 2023, and within 2 to 3 months, she experienced additional weight loss of 6 kg, representing a 21.4% decrease in weight from her peak weight of 78.4 kg in October 2022. Surveillance scans in December 2023 confirmed continued treatment response to alectinib while on concurrent semaglutide with no evidence of leptomeningeal carcinomatosis. Weight gain can be associated with metabolic syndromes such as high cholesterol and triglycerides and patient's cholesterol level had been <200 mg/dl and triglyceride <150 mg/dl. However, in January 2024, after approximately seven months of treatment with semaglutide, she was seen at an outside institution for acute gallstone pancreatitis suspected to be triggered by semaglutide which was subsequently discontinued. At her follow-up visit in May 2024, she had regained about 10 kg since stopping treatment with semaglutide. Her weight has since plateaued at 73.7 kg, representing a 19.6% increase in weight from her lowest weight on semaglutide despite continued efforts to engage in lifestyle modifications. However, we continue to closely monitor patient's weight and if the weight gain recurs in the future given patient will be on alectinib for a long future, we may have to re-initiate GLP-1 agonists.

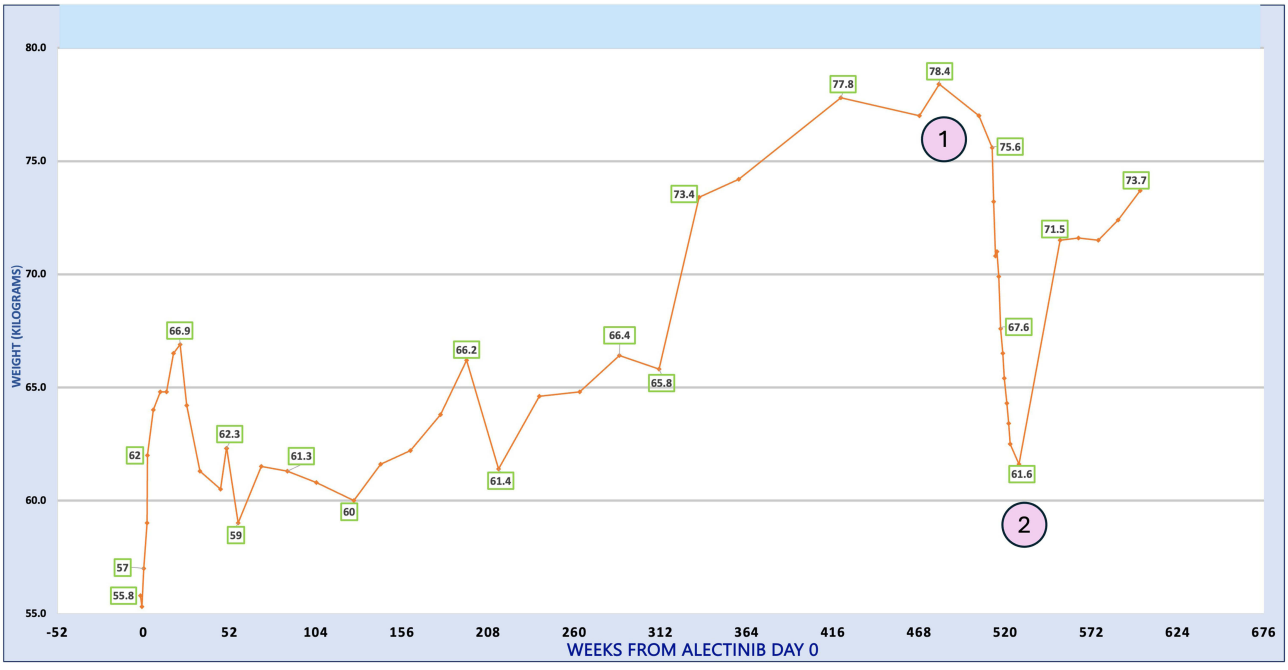

Figure 1 Time graph of the weight change of our patient during >12 years of alectinib treatment and start of start and stop of semaglutide. Circle 1 represents the start of semaglutide and circle 2 represents the end of semaglutide use.

Discussion

This case report not only serves as an important update to our 2015 case report, updating our patient's dramatic and prolonged durable response of cytology-positive leptomeningeal carcinomatosis to alectinib but also highlights side effects after prolonged use of ALK TKI in a new era where targeted therapy can in certainly rare but serendipitous situations convert a deadly disease to a chronic disease.[10] Our patient has no evidence of disease after 12 years of continuous alectinib treatment. Furthermore, our patient's extra-cranial disease has been in remission. However, our young female patient endured the physical, metabolic, social, and psychological complications related to the 29.2% increase (57 kg to 73.7 kg) in weight compared to her baseline weight since starting alectinib over twelve years ago. We must caution that our patient has been on the 750 mg twice daily dose that mirrored the US phase 1–2 dose escalation to 900 mg twice daily.[11] Although there may not seem to be a dose dependent increase in weight gain,[3] 750 mg twice daily alectinib may further exacerbate the weight gain compared to the 600 mg twice daily dose.

Although alectinib is generally well tolerated, weight gain occurred in 10% of patients in the initial analysis of ALEX.[12] Another phase 3 trial, ALESIA, which compared alectinib 600 mg BID to crizotinib 250 mg BID among Asian (Chinese, Korean, Thai) patients reported an 18% weight gain (3% grade 3, based on 14.7 months of duration of treatment [DOT] with alectinib) that increased to 31.2% (8.8% grade 3; based on much longer 42.3 months of median DOT with alectinib).[13,14] It is true that sometimes we focus more so on the traditional adverse events and sometimes significance of the less conspicuous adverse events can escape our attention.

Furthermore, among the many gastrointestinal side effects known to be associated with semaglutide is delayed gastric emptying, which could alter the absorption and thus efficacy of TKIs. Professor Dingemans' group performed a small-scale study of 10 patients with co-administration of alectinib and 1 single subcutaneous injection of semaglutide 2.0 mg and found that average alectinib exposure decreased by 32%.[15] However, the dosing of semaglutide requires every monthly stepwise dose escalation from 0.25 mg to eventual 1.7 mg or 2.4 mg over a period of several months to mitigate the delayed gastric emptying effect of semaglutide and likely lower absorption of alectinib. Thus, decrease in alectinib dose level with one injection of semaglutide is not unexpected given the immediate delayed gastric emptying but semaglutide requires slow step-up dosing and not approved for 1 single bolus subcutaneous injection. Instead, we have proposed a more prolonged pharmacokinetic study between the interaction of alectinib and semaglutide or other incretin receptor agonists.[8]

Recently, there were two case reports on the use of semaglutide to manage weight gain and hyperlipidemia associated with lorlatinib. No side effects were reported from the 2 patients, but the duration of semaglutide use was not reported.[16] Most recently, dual GLP-1/GIP agonist, tirzepatide, has demonstrated superior efficacy in percentage weight loss and decrease in waist diameter over semaglutide, a mono GLP-1 agonist.[17] Thus, in the likely future, tirzepatide is expected to be the main incretin receptor agonists used for weight management during treatment with alectinib and lorlatinib. In our patient's case if her weight gain resumes in an upward trajectory, we will likely initiate tirzepatide instead of semaglutide.

Our patient developed gallstone pancreatitis after a few months on semaglutide and underwent cholecystectomy. Obesity is a risk factor for cholelithiasis[18] so cholelithiasis and cholangitis may be increased with GLP-1 agonists use and may lead to pancreatitis secondary to cholethiasis in our patient case. We do not have CT evidence of gallstones in our patient. There is scant literature about any increased risk of pancreatitis associated with semaglutide.[19,20] Nonetheless, a baseline ultra-sound of gall bladder may be advisable before the start of GLP-1 agonists. GLP-1 agonists usage carries many side effects that we should be familiar with and collaborate with our endocrinology colleagues in the management of our patients who will likely be on long term ALK TKIs given their efficacy. More systemic studies of interaction of GLP-1 agonists and various ALK TKIs are urgently warranted.

Acknowledgment

We thank our patient and her family for their trust in our medical management. Patient signed consent for her case to be presented and published at congresses and manuscript. Given this is a single patient case report, it is not considered systemic research and did not require IRB (institutional) approval for publication of the case details.

Disclosure

Dr Zhaohui Arter is on an advisory board for J&J, Catalyst, and Rigel, outside the submitted work. Dr Misako Nagasaka reports personal fees from AstraZeneca, Daiichi Sankyo, Regeneron, Boehringer Ingelheim, Eli Lilly, Johnson and Johnson, Pfizer, Takeda, Bristol Myers Squibb, Caris; non-financial support from AnHeart/ Nuvation Bio, outside the submitted work. Dr Sai-Hong Ou reports stock ownership from MBrace Therapeutics, BlossomHill Therapeutics, Nuvalent and Lilly; stock option from Nuvation Bio; personal fees from Pfizer, outside the submitted work. The authors report no other conflicts of interest in this work.

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