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Effects of semaglutide on the exposure of alectinib in patients with NSCLC

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Background

Alectinib serves as a preferred first-line treatment for advanced anaplastic lymphoma kinase–positive (*ALK+*) non-small cell lung cancer (NSCLC), offering durable efficacy. Nonetheless, its side effect of substantial weight gain poses serious health risks for patients. Semaglutide, a highly effective glucagon-like peptide 1 receptor agonist (GLP-1RA) for treating obesity, shows potential for mitigating alectinib-induced weight gain. However, its mechanism may also impact alectinib absorption, warranting investigation into a potential drug-drug interaction, given alectinib's exposure-response relationship (Groenland et al., Clin Pharmacol Ther 2021).

Methods

In this prospective crossover study, patients with *ALK+* NSCLC receiving alectinib as standard of care, were sequentially treated with alectinib alone and alectinib combined with a single subcutaneous dose of semaglutide (2.0 mg) for both seven days. Plasma samples were collected for pharmacokinetic analysis after each week, while toxicity was also assessed. The primary endpoint was the alectinib exposure (area under the curve; $AUC_{0\text{-}10h}$), with secondary endpoints including the minimum concentration (C_{trough}), maximum concentration (C_{max}), and toxicity.

Results

In 10 patients, co-administration of semaglutide significantly reduced alectinib $AUC_{0\text{-}10h}$ by 32% (95% confidence interval (CI): -45% to -15%; $p = 0.004$) compared to alectinib monotherapy. Semaglutide also decreased C_{trough} and C_{max} by 25% (95% CI: -46% to 3%; $p = 0.072$) and 36% (95% CI: -48% to -20%; $p = 0.001$) respectively, with fewer patients maintaining efficacy threshold levels (i.e. 435 ng/mL; 60% vs 100%). Additionally, combination therapy resulted in more overall toxicity (5 versus 25 events), predominantly grade 1 or 2 gastrointestinal side effects.

Conclusions

Our study reveals a clinically relevant and significant decrease in alectinib exposure with semaglutide co-administration, emphasizing the importance of caution due to a potential negative impact on alectinib effectiveness. Consequently, monitoring alectinib plasma concentrations in patients receiving semaglutide is crucial to ensure optimal exposure and treatment outcomes. Potentially, other GLP-1RAs may have a similar effect on alectinib exposure.

Clinical trial identification

NL9702 (Dutch trial register).

Legal entity responsible for the study

Erasmus Medical University Centre, Rotterdam.

Funding

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Disclosure

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