TITLE: Lorlatinib exposed: A far from optimal dose

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We read with great interest the recent paper by Chen et al,\(^1\) describing exposure-response relationships for lorlatinib – both antitumor activity and adverse events – in patients with ALK-positive non-small cell lung cancer (NSCLC). While the authors (all of whom are current or former employees of the drug’s manufacturer) conclude that these analyses support both lorlatinib’s labeled dose and the approach to dose modification in the event of treatment-emergent adverse events (TEAEs), we believe the data clearly demonstrate the labeled dose to be excessive, resulting in unnecessary and avoidable off-target clinical and financial toxicities.

To start with, Chen et al confirm the absence of a relationship between administered lorlatinib dose and plasma exposure, as expressed by \(\log(C_{\text{max \ event}})\), at the tested doses. The authors confirm the relationship between exposure and toxicity. These particular TEAEs are not to be underestimated, despite their being laboratory abnormalities. Grade 3 hyperlipidemia implies total cholesterol exceeding 400 mg/dL and grade 3 hypertriglyceridemia implies total triglycerides exceeding 500 mg/dL, both of which raise the risk of acute pancreatitis, a disease with ~5% mortality when co-occurring with serum lipid elevation.\(^2\) Even when identified before acute hospitalization, the lipid-lowering therapies used to treat hypertriglyceridemia and hypercholesterolemia are not necessarily benign themselves. Finally, grade 3 weight gain represents at least a 20% increase in weight (e.g., 70 to 84 kg), a change that may, for many patients, reduce quality of life.

Clinical context is therefore needed: Lorlatinib is not approved as a curative therapy, only to delay progression of the disease. Where the intent of treatment is palliative, the goal of a therapy is to improve patients’ quality and quantity of life. Bearing this goal firmly in mind, are lorlatinib’s added risks, undertaken at least partially due to overdosing, compensated for by an increase in efficacy? Do the
marginal benefits of a higher lorlatinib dose outweigh the marginal risks? The null impact of lorlatinib exposure on efficacy – that is absent marginal benefit – strongly suggests that the answer for the medical oncologist and patient is ‘no’.

Furthermore, as discussed by Chen et al and others, there are multiple other treatment options for ALK-positive NSCLC disease, none of which cause the metabolic toxicities observed with lorlatinib: alectinib, brigatinib, ceritinib, and crizotinib. But perhaps the most apt comparison for lorlatinib, independent of target, is the KRASG12C-targeted small molecule sotorasib. Sotorasib lacks even a dose-concentration relationship, while simultaneously possessing a dose-toxicity relationship and lacking a dose-efficacy relationship. Like sotorasib, lorlatinib is very likely overdosed, leading to marginal increases in clinical toxicity not compensated for by any increased efficacy.

Finally, it is highly likely that if lorlatinib were being considered for approval today, the FDA would require dose optimization prior to initiating a registration trial, probably through a randomized dose-ranging trial, aiming to maximize the anticancer activity and minimize the off-target metabolic liabilities. Notably, other employees of lorlatinib’s manufacturer are supportive of this concept. The optimal lorlatinib dose is unknown, but given the drug’s dose-dependent autoinduction, significant interindividual pharmacokinetic variability and flat exposure-efficacy relationship, it is likely that a dose < 50% that of the labeled 100mg dose would maintain activity while significantly reducing off-target toxicities. Publicly- or payer-funded clinical trials testing this hypothesis are indicated. The manufacturer could also consider funding such a trial, aiming to improve their share of this highly competitive market by improving lorlatinib’s therapeutic index.

References


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