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Lorlatinib Tolerability and Association With Clinical Outcomes in Patients With Advanced ALK- or ROS1-Rearranged NSCLC: A Brief Report

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ABSTRACT

Introduction: Treatment with lorlatinib for patients with advanced ALK- and ROS1-rearranged NSCLC (ALK+ and ROS1+ NSCLC) is associated with a unique set of adverse events (AEs) often requiring dose reduction. However, the impact of dose reductions on outcomes remains unclear and is mainly limited to analyses from prospective studies of lorlatinib in the first-line setting.

Methods: We reviewed the course of 144 patients with advanced ALK- or ROS1-rearranged NSCLC treated with lorlatinib in the second-line or later setting to assess the frequency of dose reductions resulting from treatment-related AEs (TRAEs) and the association between dose reductions and progression-free survival (PFS) and overall survival (OS).

Results: A total of 58 patients (40%) had TRAE-related dose reductions, most (59%) owing to neurocognitive AEs or neuropathy. Among all patients, the median PFS was 8.1 months (95% confidence interval [CI]: 6.4–11.8); the median OS was 20.7 months (95% CI: 16.3–30.5). Among patients who were started on lorlatinib 100 mg/d (n = 122), a Cox regression model with the occurrence of a dose reduction as a time-dependent covariate indicated no association between dose reduction and PFS (hazard ratio = 0.86, 95% CI: 0.54–1.39) or OS (hazard ratio = 0.78, 95% CI: 0.47–1.30).

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Conclusions: Lorlatinib dose reductions were not associated with inferior clinical outcomes in this multicenter analysis. Prompt identification of lorlatinib TRAEs and implementation of dose reductions may help maximize tolerability without compromising outcomes.

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Keywords: Non-small cell lung cancer; ALK; ROS1; Lorlatinib; Toxicity

Introduction
Lorlatinib is a potent and selective ALK and ROS1-directed tyrosine kinase inhibitor (TKI) approved by the U.S. Food and Drug Administration for the treatment of advanced ALK-rearranged NSCLC (ALK+ NSCLC) in patients with no previous systemic therapy or progression on previous ALK TKI therapy. Lorlatinib is also included in the National Comprehensive Cancer Network guidelines as a treatment recommendation for patients with advanced ROS1-rearranged (ROS1+) NSCLC after progression on crizotinib. Compared with other ALK and ROS1 inhibitors, lorlatinib is associated with a distinct spectrum of treatment-related adverse events (TRAEs), including hyperlipidemia, peripheral neuropathy, and neurocognitive effects. In most cases, lorlatinib TRAEs are managed with either temporary dose interruptions or reductions; however, the observed frequencies of lorlatinib TRAE-related dose reductions have varied across clinical contexts, including clinical trial versus real-world settings, and the impact of lorlatinib dose reductions on long-term clinical outcomes remains unclear. To address these questions, we assembled a multicenter cohort of patients treated with lorlatinib in the second-line setting or later to provide insight into the spectrum of lorlatinib TRAEs, frequency of dose reductions, and association of dose reductions with long-term clinical outcomes.

Materials and Methods
We retrospectively identified patients with advanced ALK+ or ROS1+ NSCLC who initiated lorlatinib between October 2015 and July 2021 at the Memorial Sloan Kettering Cancer Center (New York, NY), the University of California Irvine Comprehensive Cancer Center (Orange, CA), Levine Cancer Institute (Charlotte, NC), and Winship Cancer Institute at Emory University (Atlanta, GA). Patients were identified by prescription database searches at all sites. Medical records were reviewed to identify baseline clinical and demographic features, start date and dose of lorlatinib, dates and dose of lorlatinib dose reduction and/or discontinuation, adverse events (AEs) leading to dose reduction and/or discontinuation, and dates of progression and/or death. Progression-free survival (PFS) was calculated from the date of lorlatinib start to investigator-assessed radiographic or clinical progression of disease, and overall survival (OS) was calculated from the date of lorlatinib start to the date of death. Patients were censored for PFS and OS at the date of last known follow-up if they had not progressed or died, respectively. Patients followed primarily at each clinical site were included only when at least one follow-up clinic visit note after lorlatinib initiation was available for review. For patients who were started on lorlatinib at a participating clinical site, treated at other clinical sites in the interim, and then returned to the treating physician at the participating clinical site at a later point in time, only patients with detailed interval lorlatinib dosing information were included. Patients who were followed at other sites and returned to the treating physician at the participating clinical site without detailed interim dosing information were excluded. The study was approved as a retrospective research protocol by institutional review boards at each site and met the requirements for waivers for informed consent at each site because of minimal risk to participants.

To assess the association between dose reduction and PFS and OS, time-dependent covariate Cox models were applied among patients started on lorlatinib 100 mg/d, with nonparametric hazard functions for progression and death over time constructed. All analyses were completed using R version 4.2.2 (R Core Team, Vienna, Austria).

Results

Patient Characteristics
A total of 144 patients with advanced ALK+ or ROS1+ NSCLC treated with lorlatinib were identified and included in the analysis (Table 1); 136 (94%) were treated with commercial supply, a lorlatinib expanded access program (NCT03178071), or single patient compassionate use protocol, and eight (6%) were treated on a prospective clinical trial. All patients had previously been treated with at least one TKI for advanced disease, and 42 (29%) had previously been treated with platinum-based chemotherapy. Most patients (n = 115, 80%) had ALK+ disease, and 29 (20%) had ROS1+ disease. Most patients (n = 122, 85%) were started on lorlatinib at a dose of 100 mg/d. The data cutoff date was August 16, 2022, and the median follow-up duration was 15.5 months.

Frequency and Spectrum of TRAE-Related Dose Reductions
Among all patients included in the analysis (N = 144), 58 (40%) experienced a TRAE-related dose
reduction (Table 2). The most common TRAEs associated with first dose reductions were edema (n = 14; 10%), cognitive or memory impairment (n = 11; 8%), neuropathy (n = 11; 8%), hallucinations (n = 6; 4%), and mood changes (n = 5; 3%); only one patient required dose reduction for hyperlipidemia (a case of hypertriglyceridemia). In total, dose reductions in 34 of these 58 patients (59%) were owing to neurocognitive effects (cognitive, mood, psychotic, or speech effects) or neuropathy. Eleven patients (8%) discontinued lorlatinib owing to AEs.

We next focused on patients who started on lorlatinib 100 mg/d (n = 122) (Supplementary Table 1) to minimize heterogeneity. Among these patients, 50 (41%) experienced at least one dose reduction, with a median first dose reduction to 75 mg/d. There were 18 patients (15%) who experienced at least two dose reductions, with a median second dose reduction to 50 mg/d. Two
patients (2%) experienced three dose reductions (both to 25 mg/d). The cumulative incidence estimates of first dose reduction within 6, 12, and 18 months were 33% (95% confidence interval [CI]: 24%–41%), 38% (95% CI: 29%–46%), and 41% (95% CI: 32%–49%) respectively. No patients had a dose re-escalation after dose reduction.

**Association of Dose Reductions With Clinical Outcomes**

Among all patients, the median PFS was 8.1 months (95% CI: 6.4–11.8) (Fig. 1A) and the median OS was 20.7 months (95% CI: 16.3–30.5) (Fig. 1B). Among ALK+ patients, the median PFS was 7.8 months (95% CI: 6.2–10.6) (Supplementary Fig. 1A) and the median OS was 21.2 months (95% CI: 16.3–30.5) (Supplementary Fig. 1B). Among ROS1+ patients, the median PFS was 13.7 months (95% CI: 5.7 to could not be evaluated [NA]) (Supplementary Fig. 1C), and the median OS was 20.7 months (95% CI: 14.1–NA) (Supplementary Fig. 1D).

Among the 122 patients who were started on lorlatinib 100 mg/d, dose reduction was not associated with PFS (hazard ratio = 0.86, 95% CI: 0.54–1.39, p = 0.55) (Fig. 1C) or OS (hazard ratio = 0.78, 95% CI: 0.47–1.30, p = 0.34) (Fig. 1D). There was no evidence of confounding owing to baseline patient characteristics (age, sex, genetic alteration [ALK versus ROS1], number of lines of previous therapy for metastatic disease, number of lines of previous TKI therapy for metastatic disease, and baseline Eastern Cooperative Oncology Group performance status) (Supplementary Table 2).
Discussion

The increased adoption of lorlatinib for patients with advanced ALK+ and ROS1+ NSCLC has brought to attention a unique spectrum of AEs, including neurologic, neuropsychiatric, and metabolic effects, requiring expertise in identification and management. However, data informing optimal management strategies for lorlatinib TRAEs and our understanding of the impact of these strategies on clinical outcomes remain incomplete and are largely derived from the results of prospective studies completed in the first-line setting. Here, we explored the incidence and impact of lorlatinib dose reductions in a cohort of patients treated largely in the setting of routine practice, expanded access programs, or compassionate use protocols in which there were no specific requirements for AE-related dose modifications. In this setting, approximately 40% of patients experienced a dose reduction; however, we did not identify any association between dose reduction and PFS or OS.

The rate of dose reductions identified in our study (40% overall) was generally higher than those reported in previous studies. Among patients in the phase 3 CROWN trial of first-line lorlatinib versus crizotinib in ALK+ NSCLC, 28% of patients treated with lorlatinib experienced at least one dose reduction, whereas a recent report revealed wide disparities in frequencies of dose reductions for neurocognitive AEs among patients treated with lorlatinib in the context of prospective clinical trials at the Massachusetts General Hospital (54%) versus in the registrational phase 1/2 study B7461001 (17%). The relatively high rate of dose reductions observed in our study may have been related to multiple factors, including treatment setting, and our cohort being fully comprised of patients treated in the second-line or later setting in which toxicities may be more common or difficult to manage. Regardless, our results generally support recent posthoc analyses of the CROWN trial reporting comparable 12-month PFS rates and intracranial efficacy among patients with or without early lorlatinib dose reductions in the first-line setting. Our results suggest that these observations may also be applicable in the later-line setting, extend to longer-term outcomes, and imply that there may be less incentive to continue the full-dose lorlatinib if toxicities are encountered.

Our study was limited by the lack of prospective grading and attribution of toxicities and a relatively modest sample size. In addition, inherent in this analysis, patients who experienced an early progression or death may not have had sufficient time on the drug to experience a TRAE-related dose reduction, which may have contributed to a more favorable relationship between dose reduction and the clinical endpoints.

In conclusion, we observed no association between dose reductions and long-term clinical outcomes in a multicenter cohort of patients treated with lorlatinib, despite a 41% incidence of lorlatinib TRAE-related dose reductions among patients started on 100 mg/d. Our results highlight the importance of prompt identification and management of lorlatinib TRAEs in standard clinical practice and the utility of dose reductions as an AE management tool to maximize tolerability without compromising long-term outcomes, which may have implications on choice and sequencing of available TKIs in the clinic.

CRediT Authorship Contribution Statement

Rohit Thummalapalli: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft.
Noura J. Choudhury: Conceptualization, Data curation, Investigation, Writing - reviewing and editing.
Fiona Ehrich: Formal analysis, Writing - reviewing and editing.
Tyler Beardslee: Data curation.
Danielle Brazel: Data curation.
Shannon S. Zhang: Data curation.
Shelby Merchant: Data curation.
Monica F. Chen: Data curation.
Glenn Heller: Conceptualization, Formal analysis, Methodology, Writing: reviewing and editing.
Suresh S. Ramalingam: Conceptualization, Writing - reviewing and editing.
Sai-Hong Ignatius Ou: Conceptualization, Writing - reviewing and editing.
Kathryn F. Mileham: Conceptualization, Writing - reviewing and editing.
Gregory J. Riely: Resources, Conceptualization, Formal analysis, Writing - reviewing and editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100546.

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