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PRACTICAL APPROACH

Consensus Recommendations for Management and Counseling of Adverse Events Associated With Lorlatinib: A Guide for Healthcare Practitioners

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ABSTRACT

Resistance to first- and second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) and development and progression of central nervous system metastases remain significant issues in the treatment of ALK-positive non-small-cell lung cancer. Lorlatinib is a novel third-generation ALK TKI that is able to penetrate the blood-brain barrier and has broad-spectrum potency against most known resistance mutations that can develop during treatment with crizotinib and second-generation ALK TKIs. The safety profile of lorlatinib is distinct from those of other ALK TKIs. Adverse events are typically mild to moderate in severity, seldom result in permanent discontinuations, and are generally manageable through lorlatinib dose modifications and/or standard medical therapy. This article provides guidance to advanced practice providers (e.g., nurses, nurse practitioners, physician assistants) and oncology pharmacists for the clinical management of key lorlatinib-emergent adverse reactions (i.e., hyperlipidemias, central nervous system effects, bodyweight increase, edema, and peripheral neuropathy). As lorlatinib is both a substrate and inducer of the CYP3A enzyme system and is contraindicated with strong CYP3A inducers, relevant drug-drug interactions are also highlighted.

Keywords: Lorlatinib; Non-small cell lung cancer; Safety; Therapy management

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Key Summary Points

Despite the development of second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs), emergence of resistance and central nervous system progression remain clinically significant problems in ALK-positive non-small-cell lung cancer.

Lorlatinib is a potent, brain-penetrant, third-generation, macrocyclic ALK/ROS1 TKI, with broad-spectrum potency against most known ALK resistance mutations that can develop during treatment with crizotinib and second-generation ALK TKIs.

This article provides recommendations to advanced practice providers (e.g., nurses, nurse practitioners, physician assistants) and oncology pharmacists for the clinical management of key adverse reactions reported with lorlatinib.

INTRODUCTION

The availability of targeted first- and second-generation tyrosine kinase inhibitors (TKIs), such as crizotinib (Xalkori®), alectinib (Alecensa®), ceritinib (Zykadia®), and brigatinib (Alunbrig®), has radically shifted the therapeutic landscape for anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) [1–4]. Although these therapies are initially efficacious, most patients unfortunately develop resistance [5, 6]. Historically, treatment options after failure of second-generation ALK TKIs have been limited and have typically included platinum/pemetrexed-based chemotherapy, which has shown modest efficacy in this specific clinical scenario [7].

Lorlatinib (Lorbrena®), a highly potent, third-generation ALK TKI with broad *ALK* mutational coverage that was designed to be able to penetrate the blood-brain barrier [8, 9, 10], represents a therapeutic option to fulfill this clinical need. In an ongoing phase 1/2 study (NCT01970865), lorlatinib has shown clinical activity among patients with ALK-positive metastatic NSCLC including those with central nervous system (CNS) metastases and/or prior treatment with a range of ALK TKIs [11, 12]. In November 2018, the US Food and Drug Administration granted lorlatinib accelerated approval for the treatment of patients with ALK-positive metastatic NSCLC following disease progression on crizotinib and at least one other ALK TKI or for treatment of patients with disease progression on alectinib or ceritinib as the first ALK TKI for metastatic disease. In May 2019, the European Commission also approved the use of lorlatinib in these patient populations. This indication is based on tumor response rate and duration of response; continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

SAFETY: OVERVIEW

Although generally well tolerated, lorlatinib has a distinct safety profile, with hyperlipidemias (i.e., hypercholesterolemia and hypertriglyceridemia), CNS effects, bodyweight increase, edema, and peripheral neuropathy being among the most common treatment-emergent adverse events [13]. Adverse events are usually mild to moderate in severity, seldom result in permanent discontinuations (8% of patients receiving lorlatinib 100 mg once daily [QD] discontinued lorlatinib due to adverse events), and are generally manageable through dose modification and/or standard medical therapy [11–14].

On April 7, 2018, a group of 11 multidisciplinary healthcare practitioners (HCPs), most of whom participated in the lorlatinib phase 1/2 study, met to discuss best practices for counseling, monitoring, and managing lorlatinib-emergent adverse events based on their clinical experience. The group, which included six nurse practitioners/nurses, one physician assistant, and four pharmacists, addressed key questions to provide expert consensus opinion.

This article summarizes the recommendations made by this multidisciplinary group to provide guidance to advanced practice providers (e.g., nurses, nurse practitioners, physician assistants) and oncology pharmacists regarding the management of key lorlatinib-emergent adverse events. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. An overview of the safety profile of lorlatinib will be provided, using pooled data from 332 patients who received lorlatinib at any dose (10–200 mg daily) in the phase 1/2 study, of whom 295 received lorlatinib at the recommended dose of 100 mg QD [13]. The potential for drug-drug interactions with lorlatinib will also be explored, to highlight certain medications that should be used with caution when managing lorlatinib-emergent adverse events.

Hyperlipidemias

Of the 295 patients who received lorlatinib 100 mg QD, 292 had at least one on-study assessment of serum cholesterol and triglyceride levels. Among these patients, hypercholesterolemia and hypertriglyceridemia were reported in 96% and 90% of patients, respectively (Table 1) [13]. Primarily grade 1 or 2 in severity, hyperlipidemias were the most common adverse event reported with lorlatinib, with onset typically within the first few weeks of treatment (median time to onset 15 days [range 1–219 days]) [15]. Although a high percentage of patients required medical intervention (80% of patients who received lorlatinib at any dose in the phase 1/2 study received at least one lipid-lowering agent), hyperlipidemias were generally manageable and rarely resulted in temporary discontinuation (7%) or dose reduction (3%) [13].

A cardio-oncology consultation is recommended, particularly for patients with a history of cardiovascular disease, to establish reasonable goals for cholesterol levels. Lipid monitoring should be included with routine laboratory testing/bloodwork, with lipid levels assessed at baseline, at the first follow-up visit (or within

Table 1 Common adverse events (i.e., those occurring in ≥ 10% of patients) and common laboratory abnormalities (i.e., those occurring in ≥ 20% of patients) with lorlatinib 100 mg once daily [13]

	Pooled lorlatinib 100 mg once daily (N = 295)	
	All grades (%)	Grade 3/4 (%)
Adverse events		
Psychiatric effects		
Mood effects[a]	23	2
Nervous system effects		
Peripheral neuropathy[a]	47	3
Cognitive effects[a]	27	2
Headache	18	0.7
Dizziness	16	0.7
Speech effects[a]	12	0.3
Sleep effects[a]	10	0
Respiratory effects		
Dyspnea	27	5
Cough	18	0
Ocular effects		
Vision disorder[a]	15	0.3
Gastrointestinal effects		
Diarrhea	22	0.7
Nausea	18	0.7
Constipation	15	0
Vomiting	12	1
Musculoskeletal and connective tissue effects		
Arthralgia	23	0.7
Myalgia[a]	17	0
Back pain	13	0.7
Pain in extremity	13	0.3
General effects		
Edema[a]	57	3
Fatigue[a]	26	0.3

Table 1 continued

	Pooled lorlatinib 100 mg once daily (N = 295)	
	All grades (%)	Grade 3/4 (%)
Weight gain	24	4
Pyrexia	12	0.7
Infections		
Upper respiratory tract infection[a]	12	0
Skin effects		
Rash[a]	14	0.3
Laboratory abnormalities		
Chemistry		
Hypercholesterolemia[b]	96	18
Hypertriglyceridemia[b]	90	18
Hyperglycemia[c]	52	5
Increased aspartate aminotransferase[b]	37	2
Hypoalbuminemia[d]	33	1
Increased alanine aminotransferase[b]	28	2
Increased lipase[e]	24	10
Increased alkaline phosphatase[b]	24	1
Increased amylase[f]	22	4
Hypophosphatemia[b]	21	5
Hyperkalemia[c]	21	1
Hypomagnesemia[b]	21	0
Hematology		
Anemia[c]	52	5
Thrombocytopenia[c]	23	0.3
Lymphopenia[b]	22	3

Graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

[a] Clustered terms comprising adverse events that represent similar clinical symptoms/syndromes

[b] N = 292

[c] N = 293

[d] N = 291

[e] N = 290

[f] N = 284

1 month of initiating treatment), at 2 months, and approximately every 3 months thereafter during lorlatinib treatment (Table 2). At the onset of elevated cholesterol (upper limit of normal–300 mg/dl [upper limit of normal–7.75 mmol/l]) and/or triglycerides (150–300 mg/dl [1.71–3.42 mmol/l]), treatment should be initiated with a preferred statin, based on the drug interaction potential (Table 3) [16]. Rosuvastatin (Crestor®) is the only high-intensity statin recommended for lorlatinib-associated hyperlipidemias based on its low involvement with CYP450 enzymes that are able to interact with lorlatinib. With effective lipid management, dose modifications of lorlatinib are unlikely. Dose interruptions are recommended only for severe hyperlipidemic events (grade 4: cholesterol levels > 500 mg/dl and/or triglyceride levels > 1000 mg/dl), despite the use of lipid-lowering therapies. In these cases, lorlatinib should be withheld until cholesterol is reduced to ≤ 400 mg/dl and triglycerides to ≤ 500 mg/dl (i.e., grade ≤ 2) before rechallenging at the same dose. If elevated cholesterol and/or triglyceride levels recur, the lorlatinib dose can be reduced (Table 2). If lipid levels remain elevated or uncontrolled, more frequent monitoring may be required, with consideration made for the

Table 2 Management of selected lorlatinib-emergent adverse events

	Monitoring	Management	Resources
Hyperlipidemias	Baseline	Consultation with cardio-oncologist	For HCPs
	First follow-up visit (or $\leq$ 1 month)	Statin (preferred pitavastatin, pravastatin, or rosuvastatin)	List of preferred statins
	2 months	Lorlatinib interruption if cholesterol $>$ 500 mg/dl and/or triglycerides $>$ 1000 mg/dl (i.e., grade 4). Rechallenge at same dose when hyperlipidemia severity reduces to grade $\leq$ 2	For patients
	Every 3 months		Patient-targeted educational websites
			Healthy recipe list
		Lorlatinib dose reduced if recurs	List of foods to avoid
CNS effects	Baseline	MRI	For HCPs
	First follow-up visit	Referral to psychiatrist or therapist	Cognitive assessment tool to be used by advanced HCP or self-reported
	6 weeks	Review concomitant medications	
	At each visit (or $\leq$ 3 months)	Consider lorlatinib interruption for grade 1. Resume at the same or lower dose upon recovery	For patients
		Lorlatinib interruption for grade 2–3. Resume at reduced dose upon recovery to grade $\leq$ 1	Reminder function on smartphones
		Permanent discontinuation of lorlatinib for grade 4	Smartphone apps to track mood changes
Body weight increase	At each visit	Lifestyle modifications (e.g., diet, exercise)	For patients
		Referral to a nutritionist or oncology-certified dietician	Diet/exercise advice
		In more severe cases (grade $\geq$ 3), lorlatinib interruption. Resume at reduced dose upon improvement	Bimonthly check-ins with a nutritionist
			Smartphone apps for tracking steps or activity
			Food diary
			Meal planning support
			Simple, healthy recipes

Table 2 continued

	Monitoring	Management	Resources
Edema	At each visit	Compression stockings Leg elevations Exercise Reduction of salt intake Referral to an oncology-certified dietician Diuretic (usually furosemide) if edema is substantially disruptive to quality of life or for pulmonary edema Consider lorlatinib dose reduction or interruption for persistent edema despite intervention or for more severe cases; rechallenge at reduced dose	For patients Educational pamphlet with a description of foods that are high in salt Recipes that are low in salt Nutrition counseling
Peripheral neuropathy	6–8 weeks At each visit	Consider lorlatinib dose reduction for persistent grade $\leq$ 2 events Lorlatinib interruption for grade $\geq$ 3. Rechallenge at reduced dose upon improvement Standard medical therapies (e.g., vitamin B_1, vitamin B_6) Standard neuropathy medications (e.g., gabapentin, pregabalin)[a]	For HCPs Peripheral neuropathy assessment tool Pocket card with checklist of symptoms

CNS central nervous system, *HCP* healthcare professional, *MRI* magnetic resonance imaging
[a] Caution is recommended before initiating analgesics with central nervous system toxicities

Table 3 Recommended statins for the treatment of lorlatinib-associated hyperlipidemias [15]

Drug	Dosing
Pitavastatin	2 mg once daily (orally)
Pravastatin	40 mg once daily (orally)
Rosuvastatin	5–10 mg once daily (orally; moderate-intensity therapy) 20–40 mg once daily (orally; high-intensity therapy)

Recommendations are based on the potential risk of drug-drug interactions

patient's cardiovascular risk, age, overall health, and pre-existing conditions.

In addition to medication management, advanced practice providers and/or pharmacists can play an important role in care by counseling the patient. The patient should be reassured that although there is a high likelihood that a statin will be prescribed to manage lipid levels, this adverse event is generally manageable through lipid-lowering therapy and/or lorlatinib dose modifications. Patients may also be empowered to assume an active role in ensuring lipid levels are routinely monitored.

Advanced practice providers and pharmacists can also refer patients to patient-targeted

Table 4 Common central nervous system effects in patients receiving lorlatinib treatment

	Common manifestations	Median time to onset (range), days
Cognitive effects	Memory impairment	53 (1–423)
	Cognitive disorder	
	Amnesia	
Mood effects	Irritability	43 (1–452)
	Anxiety	
	Depression	
	Affect lability	
Speech effects	Perception of slowed speech	42 (1–404)
	Difficulty in word finding	

educational websites and provide a list of healthy recipes or foods to avoid. In addition, advanced practice providers and pharmacists can support patients and caregivers by communicating changes in cholesterol and triglyceride levels, and/or changes in treatment approach, to all HCPs involved in the patient's care. Pharmacists can help educate patients at the onset of therapy about the risk of hyperlipidemias and the possibility of statin treatment and can empower patients to make sure their HCPs monitor lipid levels during check-ups. Pharmacists, in particular, may also play a pivotal role in mitigating the challenges associated with lorlatinib drug-drug interactions.

Central Nervous System Effects

A broad spectrum of CNS effects has been observed in patients receiving lorlatinib, including seizures, hallucinations, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep. Fifty-four percent of patients who received lorlatinib at any dose experienced at least one of these adverse events [13]. In the pooled safety analysis of patients treated with lorlatinib at a dose of 100 mg QD, the most frequently reported CNS effects were changes in cognitive function (27%), mood (23%), and speech (12%) (Table 1) [13]. These CNS effects typically presented within the first 2 months of treatment (Table 4) and were generally mild in severity, intermittent, and reversible upon dose modification [15].

At the onset of lorlatinib treatment, HCPs on the oncology team should counsel patients about the possibility of CNS effects and provide educational resources about these effects. In particular, the potential for mood changes should be discussed with patients, especially those who have pre-existing psychiatric conditions. In addition, family and caregiver(s) should be included in the patient's initial education and counseling, as they are most likely to notice the onset of more mild-to-moderate changes. When counseling patients and caregivers on CNS effects, it is essential to define the effects as cognitive, mood, or speech changes and to use simple descriptive terms (e.g., changes in mood or irritability, problems with memory, or slowed/slurred speech). It is also important to reinforce that CNS effects are typically mild, manageable, and reversible.

Patients should be assessed for mood and cognition before initiating lorlatinib and should be monitored by the entire healthcare team and by their caregiver(s) thereafter during treatment. Regular monitoring should be undertaken at the first follow-up visit, at 6 weeks, then at each of the patient's regular visits (or at least every 3 months) (Table 2). Patients should

be encouraged to call if any changes occur between visits, and may be referred to supportive care providers (e.g., palliative care specialists, psychiatrists, psychologists) for further support. Special consideration must be given to patients without a primary caregiver; these patients should receive frequent calls to inquire about changes and should be referred to outside resources (e.g., therapists, social workers).

At the onset of a CNS effect, HCPs should consider different approaches for management before adjusting the dose of lorlatinib (Table 2). Strategies may include temporarily stopping lorlatinib to monitor the adverse event, contacting a psychiatrist or therapist, or conducting magnetic resonance imaging to evaluate for brain metastases. Concomitant medications should also be considered as a potential contributing factor. HCPs should consider the impact of the adverse event on the patient's daily life and their willingness to reduce the lorlatinib dose. When considering a dose reduction, it is important to recall that in the phase 1/2 study, permanent discontinuation of lorlatinib for CNS effects was rare (only 1.5% of patients who received lorlatinib at any dose) and that temporary discontinuation or dose reduction was uncommon (< 10%) [13].

The most appropriate method for managing a CNS effect depends on the severity of the adverse event. Mild events (grade 1) may simply be managed by a brief dose interruption with resumption at the same or lower dose upon recovery. Moderate events (grade 2 or 3) necessitate a temporary discontinuation until symptoms resolve to grade $\leq$ 1, with resumption at a reduced dose. The occurrence of a severe event (grade 4) should result in permanent discontinuation of lorlatinib [13, 15]. Resources to help with management of CNS effects include cognitive assessment tools that can be self-reported or administered by HCPs, reminder functions on smartphones, and smartphone apps that can track mood changes between office visits (Table 2).

Advanced practice providers and pharmacists can enhance the care of patients who experience CNS effects by ensuring that CNS changes are effectively communicated to all HCPs and by working with other specialists or supportive care providers as needed to monitor and manage CNS effects. In addition, advanced practice providers and pharmacists can provide support by calling patients during treatment to inquire about CNS effects.

Bodyweight Increase

In the pooled safety analysis of patients who received lorlatinib 100 mg QD, 24% had weight gain that was reported as an adverse event, most of which were grade 1 or 2 in severity (Table 1) [13], and 30.9% and 13.5% had bodyweight increases of 10–20% or > 20% from baseline, respectively [15]. Dose interruptions or reductions associated with bodyweight increase were infrequent, with only two incidents of each occurring. Bodyweight increase typically presented within 2 months of initiation of lorlatinib (median time to onset, 64 days [range 1–519 days]) [2]. Although causality has not been determined, bodyweight increase may be linked to increased appetite.

Increased appetite has been reported by some patients, suggesting that bodyweight increase may potentially be associated with increased food intake; however, causality has not been determined [15]. When counseling patients, HCPs on the oncology team should advise on the risk of weight gain while receiving lorlatinib. This should be explained to patients at the start of treatment, and the importance of lifestyle modifications, such as diet and moderate exercise, should be emphasized in the event of an increase in bodyweight. Recommendations for the level and amount of exercise should be personalized for each patient based on their ability and interest.

Bodyweight should be monitored by the healthcare team at each patient visit while receiving lorlatinib. In the event of a bodyweight increase, patients should be referred to a nutritionist or dietician, if available, and/or encouraged to implement weight reduction activities such as diet and moderate exercise, as appropriate. Lifestyle modifications are preferred over lorlatinib dose reductions (Table 2).

Advanced practice providers and pharmacists are ideally positioned to provide patients

and caregivers with weight management resources to support patient needs. Appropriate resources for managing weight gain include diet/exercise advice, bimonthly check-ins with a nutritionist, apps that can track steps or activity, a food diary, meal planning support, healthy recipes, and referral to an oncology-certified dietician (Table 2). While HCPs should use their discretion based on individual patient information (body mass index, etc.), intervention may be needed in the event of body weight increases of approximately 10%.

Edema

Edema was experienced by 57% of the patients in the pooled safety analysis who received lorlatinib 100 mg QD (Table 1) [13]. The median time to onset of edema was 42 days (range 1–232 days), and the median duration was 163 days [15]. Although events were mostly mild in severity, edema was the most common cause of dose interruptions (7%) and dose reductions (6%) [13].

At the onset of lorlatinib treatment, patients should be educated by HCPs within the oncology team about the signs and symptoms of edema using non-medical language (e.g., excess fluid, weight gain, swelling of the arms, legs, hands, and feet). Bodyweight should be monitored during each office visit (Table 2), and patients should be instructed to report any changes in the fit of rings, clothes, shoes, etc.

For mild-to-moderate edema, recommendations may include using compression stockings, leg elevations, increasing exercise, and reducing salt intake to the American Heart Association-recommended level of $\leq$ 2300 mg of sodium per day, moving towards an ideal level of $\leq$ 1500 mg per day [17]. If edema is substantially disruptive to quality of life, or signs of pulmonary edema are present, consider intervention with a diuretic such as furosemide (Lasix®) prior to reducing the lorlatinib dose (Table 2). However, if edema persists despite intervention, or if symptoms become severe, a reduction or interruption in lorlatinib dose may be necessary until resolution. Rechallenge should be initiated at a reduced dose [15].

Advanced practice providers and pharmacists can help to monitor and counsel patients about edema and should coordinate with dieticians as needed. Patients can be provided with resources to help them manage edema, such as an educational pamphlet with a description of foods that are high in salt, recipes for meals that are low in salt, and nutrition counseling. Referral to an oncology-certified dietician might also be considered (Table 2).

Peripheral Neuropathy

Lorlatinib-emergent peripheral neuropathy affected 47% of the patients who received lorlatinib 100 mg QD in the phase 1/2 study (Table 1) [13]. Events were generally reversible and mild in severity, with a median time to onset of 77 days (range 1–723 days) [15]. Although peripheral neuropathy was one of the most frequently reported adverse events associated with lorlatinib dose interruptions (5%) and dose reductions (5%), most patients responded well to these modifications [13, 15].

HCPs within the oncology team should counsel patients about peripheral neuropathy at initiation of lorlatinib. A description should be given of the types of symptoms the patient may experience, such as numbness or tingling in the fingers, and should include examples, such as difficulty buttoning shirts or jackets. The patient should be reassured that these symptoms are usually mild and reversible with a reduction in the dose of lorlatinib.

Peripheral neuropathy should be monitored by oncologists and/or advanced practice providers during a routine visit approximately 6–8 weeks after starting treatment and at subsequent follow-up visits (Table 2). At the onset of peripheral neuropathy, the severity should be assessed before considering management approaches. Reducing the dose of lorlatinib may be considered with persistent grade 1 or 2 events. Temporary discontinuation of lorlatinib is recommended for grade 3 or 4 peripheral neuropathy, with resumption at a reduced dose only when neuropathy has reduced to grade 2 or better [15]. The use of vitamin B_1, vitamin B_6, and standard neuropathy medications such as

gabapentin or pregabalin can be considered for relief of symptoms [15]. However, caution is recommended before initiating such therapy because of limited supporting literature and the potential for CNS-related adverse effects.

Multidisciplinary HCPs should work together to monitor patients for signs and symptoms of peripheral neuropathy. Potential resources that can help manage peripheral neuropathy include an assessment tool for HCPs, e.g., Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity, Total Neuropathy Score [18], or a pocket card with a checklist of symptoms to assess at each visit (Table 2).

Drug-Drug Interactions

Lorlatinib is both a net moderate inducer of CYP3A at steady state as well as a substrate of CYP3A [13]. Thus, concomitant use of lorlatinib with moderate CYP3A inducers, strong CYP3A inhibitors, and CYP3A substrates with narrow therapeutic indices should be avoided [13]. In addition, due to the potential for serious hepatotoxicity, lorlatinib is contraindicated in patients taking concomitant strong CYP3A inducers [13]. Potential therapies that could be used to treat key lorlatinib-emergent adverse events and that may interact with lorlatinib are shown in Table 5. For example, carbamazepine, an anticonvulsant sometimes used as a mood stabilizer, and St. John's wort, an herbal therapy often used to treat depressed mood, are strong CYP3A4 inducers that are contraindicated in patients receiving lorlatinib. Patients should be counseled to contact their HCP prior to starting any over-the-counter medications, vitamins, or herbal supplements because of the potential for drug interactions with lorlatinib. Similarly, the choice and dosage of statins may be based on their differential metabolism by the CYP450 pathway. If other lipid-lowering agents, such as fibrates or fish oils, are required, it is important to consider which is the most appropriate; fenofibrate has the least involvement with CYP450 enzymes, followed by fish oils and nicotinic acid [15]. Furthermore, it is important to advise females of reproductive potential to use an effective non-hormonal method of contraception as CYP3A induction by lorlatinib can render hormonal contraceptives ineffective [13].

In circumstances where concomitant use of lorlatinib with interacting medications cannot be avoided, the dose of lorlatinib or the interacting medication may need to be modified, or more frequent laboratory monitoring may be required. For instance, if concomitant use with a strong CYP3A inhibitor cannot be avoided, lorlatinib can be reduced by one dose level (i.e., 75 mg QD). If concomitant use of moderate CYP3A inducers cannot be avoided, HCPs should monitor levels of aspartate aminotransferase, alanine aminotransferase, and bilirubin 48 h after initiating lorlatinib and at least three times during the first week after initiating lorlatinib. The dosage of CYP3A substrates may also need to be increased in accordance with approved product labeling if concomitant use with lorlatinib is unavoidable.

Table 5 Examples of therapies that may interact with lorlatinib based on involvement with cytochrome P450 3A

Adverse event	Treatment
Hyperlipidemias	CYP3A4 substrates: atorvastatin, fluvastatin, lovastatin, simvastatin
Mood effects	CYP3A4 substrates: alprazolam, buspirone, citalopram, clonazepam, diazepam, escitalopram, midazolam, nefazodone, venlafaxine
	CYP3A4 inhibitors: nefazodone
	CYP3A4 inducers: carbamazepine[a], St. John's wort[a]
Edema	CYP3A4 substrates: eplerenone
Peripheral neuropathy	CYP3A4 substrates: oxycodone, tramadol

Not a comprehensive list of all possible drug interactions
CYP cytochrome P450
[a] Strong inducer of CYP3A4 and thus contraindicated with lorlatinib

DISCUSSION

We believe that oncologists, nurses, advanced practice providers, and pharmacists should counsel patients and caregivers on the most common and potentially serious side effects associated with lorlatinib, which include the potential for increased cholesterol and lipid levels; cognitive, mood, or speech changes; weight gain; edema; and peripheral neuropathy. In addition, patients need to understand that they may be prescribed a new medication, such as a statin, or may be advised to make changes to their diet and exercise routines to manage these side effects. Patients and caregivers should also be counseled that changes in mood, thinking, or speech are generally mild and reversible and that these changes typically respond to dose modifications, if needed. The importance of the role of caregivers in monitoring for these changes should be highlighted to both patients and caregivers. Proactive counseling, monitoring, and effective management of treatment-related adverse events is important for patients receiving lorlatinib.

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