Presented at Annual Meeting on Supportive Care in Cancer • June 22–24, 2017 • Washington, DC

NOVARTIS

Analysis of Drug Interaction Potential of Ribociclib With Commonly Used Medicines and Herbal Supplements in Patients With Advanced Breast Cancer

Rodney Hunter, PharmD, BCOP

Texas Southern University Cooperative Oncology Research Group at Texas Southern University College of Pharmacy and Health Sciences, Memorial Hermann-Texas Medical Center, University of Texas McGovern Medical School, Houston, TX

References

1. Kisqali [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
2. Hortobagyi GN et al. ASCO 2017. Poster 1038.
3. Alsanad SM et al. *BMC Complement Altern Med.* 2016;16(1):393.
4. Molassiotis A et al. *Complement Ther Clin Pract.* 2006;12(1):34-39.
5. Vickers KA et al. *BMC Complement Altern Med.* 2006;6:40.

Introduction

- Adequate management of comorbidities and adverse events is necessary to maximize drug exposure and treatment benefit in patients with advanced breast cancer
- Ribociclib is an orally bioavailable, selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) approved for use in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer[1]
  - Results from the second overall survival interim analysis (data cutoff, January 2, 2017) of the Phase 3 trial, MONALEESA-2 (ClinicalTrials.gov number NCT01958021), showed that treatment with ribociclib + letrozole exhibited superior progression-free survival (PFS) versus placebo + letrozole (median duration of PFS, 25.3 vs 16 months, respectively; hazard ratio, 0.568; 95% CI, 0.457–0.704; $P=9.63 \times 10^{-8}$) in postmenopausal patients with advanced breast cancer[2]
- Ribociclib is known to exhibit drug-drug interactions (DDIs) with metabolizers and substrates of cytochrome P450 (CYP) and drugs with known potential to prolong QT interval[1]
  - Ribociclib can exhibit variable exposure with medicines that induce or inhibit CYP3A
- There is inadequate awareness and communication in the literature about safe coadministration of medications and nutritional supplements with ribociclib
- Presented here is an analysis of potential DDIs of common medicines and nutritional supplements with ribociclib based on a single center's experience

Methods

- This single-center retrospective chart review of patients (n=42) with advanced breast cancer identified the most commonly used drugs and supplements from 2/1/2016 to 1/31/2017, categorized by comorbidity
- The potential for drug-drug interaction and/or QT interval prolongation was assessed using available clinical pharmacology information listed in the following databases:
  - Lexicomp Online
  - Natural Products
  - Memorial Sloan Kettering Cancer Center Integrative Medicine databases
- A variation of Stockley's Herbal Medicines Interactions was used to establish severity and recommendation for herbal product interaction with ribociclib[3]
- The pharmacodynamic interactions between medications and supplements were also evaluated for severity and clinical recommendations[4,5]
  - Interactions that involved adverse effects warranting dosing alterations were placed in the "Use with caution" and "Prohibited" categories

Results

- The most common 120 prescription medicines and 32 nutritional supplements (eg, herbal supplements, vitamins, natural foods and extracts) to treat acute symptoms (eg, nausea, pain, infections) and chronic comorbidities (eg, diabetes, hypertension, cardiovascular disease) were identified
  - Commonly used supplements had varied potential effects on ribociclib metabolism

Conclusions

- Therapies considered to be standard of care for commonly reported side effects and comorbidities in patients with advanced breast cancer can likely be safely administered with ribociclib
- Nutritional supplements can exhibit variable physiological effects when used concomitantly with ribociclib
- Patients should be advised to inform their healthcare professionals about any new medications, herbal drugs, or supplements they take or plan to take during treatment with ribociclib
- Physicians should monitor patients carefully for adverse effects from concomitant medications and supplements
- Pharmacists and physicians are advised to use individualized clinical judgment when determining the best treatment option for patients

Acknowledgments

Jayson Montgomery and Mabella Tamambang assisted with the research for this study. Support for preparation of this poster was provided by MedThink SciCom and funded by Novartis Pharmaceuticals Corporation.

Data included in this poster have been previously presented in full at Oncology Nurse Advisor Navigation Summit; June 15–17, 2017; Austin, TX.

Presenter email address:
Rodney.Hunter@memorialhermann.org

	Safe to use	Use with caution	Prohibited
Acid-reducing agents[a]	Esomeprazole, Famotidine, Omeprazole, Pantoprazole	Ranitidine (MATE1/OCT2)	
Analgesics	Celecoxib, Codeine, Ibuprofen, Meloxicam, Morphine, Naproxen, Oxycodone, Sumatriptan, Tramadol	Hydrocodone and acetaminophen (CYP3A4)	Fentanyl (CYP3A4)
Antiarrhythmic agents	Digoxin		Amiodarone (QT prolongation)
Anticholinergic/ Antihistamine agents	Cetirizine, Oxybutynin, Tolterodine		
Anticoagulation agents[b]	Aspirin, Clopidogrel, Dabigatran, Warfarin	Apixaban (CYP3A4), Enoxaparin	Rivaroxaban[c] (CYP3A4)
Antiemetics		Ondansetron, oral/sublingual 4–8 mg/dose maximum (CYP3A4, possible QT prolongation)	Ondansetron, intravenous (CYP3A4, QT prolongation)
Antihyperglycemic agents[d]	Glimepiride, Glipizide, Glyburide, Liraglutide, Pioglitazone, Saxagliptin, Sitagliptin	Metformin (GI effects)	
Antihyperlipidemia agents[e]	Ezetimibe, Fenofibrate, Gemfibrozil	Atorvastatin (CYP3A4), Rosuvastatin[f]	Simvastatin (CYP3A4)
Antihypertensive agents[g]	Atenolol, Carvedilol, Clonidine, Enalapril, Irbesartan, Labetalol, Lisinopril, Losartan, Olmesartan, Propranolol, Ramipril, Spironolactone, Valsartan	Amlodipine (CYP3A4), Diltiazem (CYP3A4), Furosemide (possible QT prolongation), Hydrochlorothiazide (possible QT prolongation), Losartan (MATE1/OCT2), Nifedipine (CYP3A4), Verapamil (CYP3A4)	Indapamide
Antimicrobial agents	Valacyclovir	Amoxicillin, Metronidazole (QT prolongation)	Azithromycin (QT prolongation), Ciprofloxacin (QT prolongation), Fluconazole (QT prolongation), Levofloxacin (QT prolongation)
Miscellaneous	Allopurinol, Carisoprodol, Cyclobenzaprine, Dexamethasone, Donepezil, Fluticasone, Gabapentin, Levothyroxine, Magnesium sulfate, Potassium chloride, Prednisone, Pregabalin, Rivastigmine, Topiramate	Albuterol (QT prolongation), Budesonide (CYP3A4), Lidocaine (CYP3A4)	
Osteoporosis treatments	Alendronate, Ibandronate, Risedronate		
Psychotropic agents	Alprazolam, Bupropion, Butalbital, Clonazepam, Duloxetine, Levetiracetam, Lorazepam, Memantine, Modafinil, Oxcarbazepine, Trazodone, Varenicline, Zaleplon, Zolpidem	Amitriptyline (possible QT prolongation), Buspirone (CYP3A4), Desvenlafaxine (CYP3A4), Eszopiclone (CYP3A4), Olanzapine (possible QT prolongation), Paroxetine (QT prolongation), Phenobarbital (CYP3A4), Phenytoin sodium (CYP3A4), Sertraline (possible QT prolongation)	Carbamazepine (QT prolongation), Citalopram (QT prolongation), Escitalopram (QT prolongation), Fluoxetine (QT prolongation), Quetiapine (QT prolongation), Venlafaxine (QT prolongation)
Nutritional supplements	Chlorella, Cranberry, Echinacea, Lycopene, Modified citrus pectin, Probiotics, Resveratrol, Selenium, Vitamin C	Coenzyme Q10, Curcumin, Flaxseed, Frankincense essential oil, Grape seed extract, Green tea[h], Indole-3-carbinol, Lugol's solution, Melatonin, Soy, Turmeric, Vitamin B complex, Vitamin D	Black cohosh (hepatotoxicity, hormonal effects), Fish oil, Gingko (palpitations, QT prolongation), Ginseng (CYP3A4, QT prolongation), Garlic, Ginger, Milk thistle, Saw palmetto, St John's wort (CYP3A4)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GI, gastrointestinal; MATE1, multidrug and toxin extrusion protein 1; OCT2, organic cation transporter 2. [a]No obvious pharmacokinetic/pharmacodynamic interactions with proton pump inhibitors and H2-receptor antagonists. [b]There is increased risk of bleeding with all the anticoagulants listed above because of ribociclib's myelosuppressive effects. [c]Depends on additional drug/group, international labeling, and renal function. [d]The listed antihyperglycemic agents do not have any pharmacokinetic interactions but may cause nausea. [e]Statins have a higher potential for myopathy complications than the other medications listed. [f]Rosuvastatin is a better alternative to simvastatin and atorvastatin because its pharmacokinetic interactions are limited. [g]Ribociclib has a peripheral edema adverse effect profile similar to calcium channel blockers (CCBs). The interaction between ribociclib and CCBs is further compounded by pharmacokinetic interactions (CYP3A4). The other drug classes (ACE inhibitors, ARBs, thiazides, loop diuretics [with the exception of indapamide], beta blockers, alpha-2 adrenergic receptor agonists) may be better alternatives. [h]Avoid prior to surgery; may cause bleeding.

Ribociclib was discovered by Novartis Institutes for BioMedical Research in collaboration with Astex Pharmaceuticals. This study was sponsored by Novartis Pharmaceuticals Corporation.