Managing Drug Interactions with Oral Oncolytics in the Management of Hematologic Malignancies

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Objectives & Disclosure

Understand the importance of recognizing and managing drug interactions in patients receiving oral oncolytics for the treatment of hematologic malignancies

Evaluate a patient's drug regimen for the presence of common drug interactions with oral oncolytics for the treatment of hematologic malignancies

Develop a plan to mitigate drug interactions in patients receiving oral oncolytics for the treatment of hematologic malignancies

Disclosure

- *I have no conflicts of interest to disclose*
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Clinical Impact of Drug Interactions

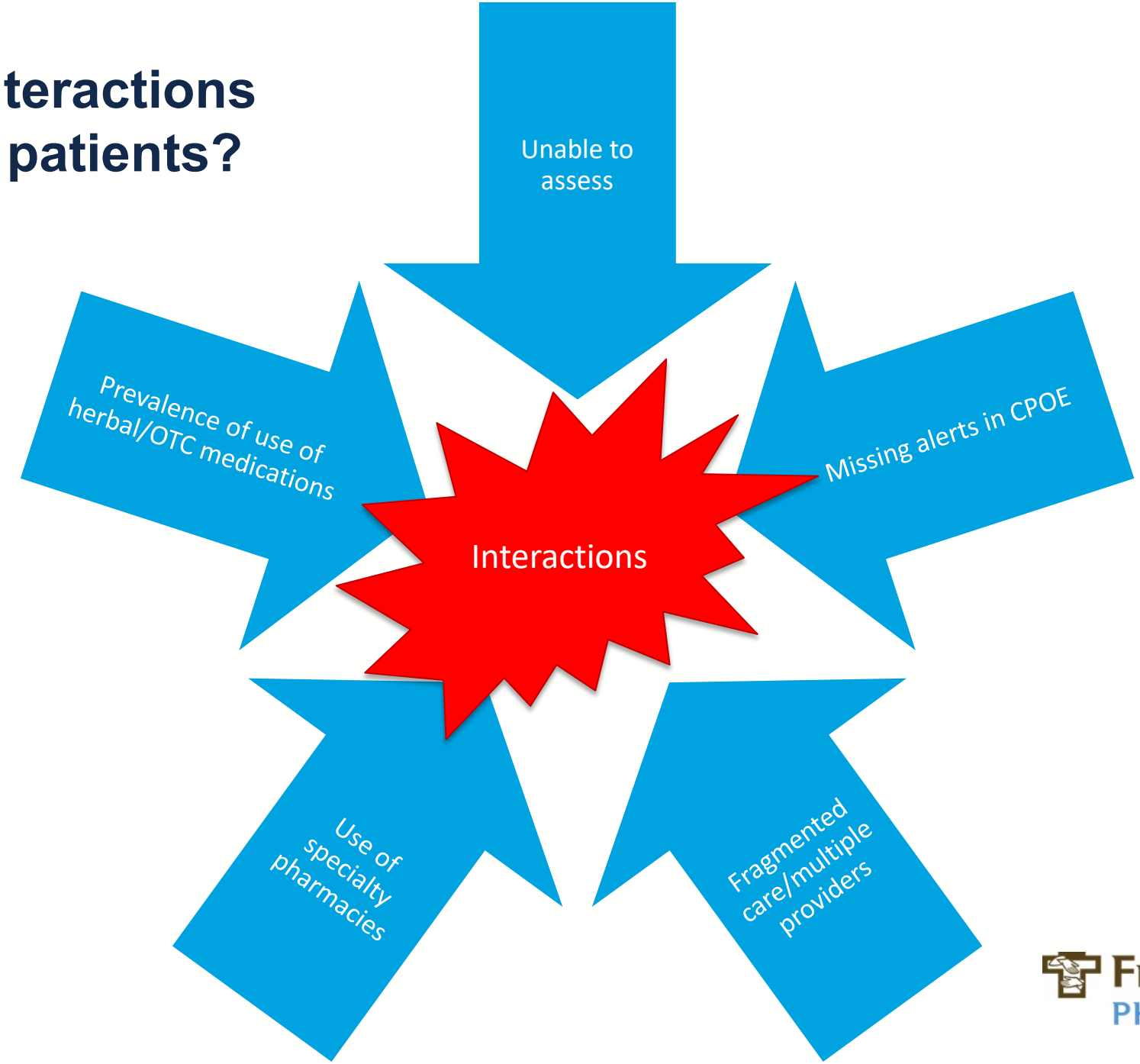
Reference	Interacting Drugs	Mechanism of Interaction	Impact of Interaction	Outcome
J Clin Pharm Pract. 2017;23:470	Idelalisib Diazepam	Idelalisib potent CYP3A4 inhibitor	Altered mental status Progressive weakness Respiratory acidosis Hospital admission Placed on BiPAP	Discharged 3 days later Lorazepam substituted for diazepam
J Clin Pharm Ther. 2016;41:104	Ibrutinib Verapamil	Verapamil moderate CYP3A4 inhibitor	Severe diarrhea Fall/LOC Hospital admission	Discharged 3 days later Olmesartan substituted for verapamil
Isr Med Assoc J. 2016;18:433	Ibrutinib Amiodarone load	Amiodarone moderate CYP3A4 inhibitor	SOB/Volume overload Echo: restrictive LV filling pattern, EF 50-55% BNP 376	Held amiodarone x 2 days and restarted at 200 mg/d Symptoms resolved
Leuk Lymphoma. 2014;55:2213	Bosutinib Warfarin Dilitiazem Lovastatin	Bosutinib inhibition of PgP led to increased levels of diltiazem/lovastatin leading to inhibition of warfarin metabolism (CYP3A4/2C9)	2 weeks after starting bosutinib – hypoxia/hemoptysis INR > 15 Pulmonary hemorrhage	Reversal of anticoagulation and methylprednisolone led to improvement
Am J Hematol. 2012;87:338	Lenalidomide Itraconazole	Itraconazole potent PgP inhibitor	Neutropenia despite dose reductions Elevated lenalidomide concentrations	Not reported
Intern Med J. 2009;39:708	Imatinib Amlodipine	Amlodipine inhibition of ABCG2 and CYP3A4	Nausea, edema Numbness in chin, b/l pain and numbness in feet	Amlodipine stopped Symptoms resolved Mild residual neuropathy resolved over 9 months

Impact of Drug Interactions

- Increased adverse effects
  - Observed in practice
  - Reported in literature
- Decreased efficacy
  - Difficult to pinpoint
  - Not reported in case reports

Reference	Study Design	Results	Hem Meds
Br J Cancer. 2013;108:1071	Retrospective review of oral anti-neoplastic drugs	N=898 patients 1359 Potential drug interactions (426 patients) 16% major or moderate severity	Imatinib – 30 Dasatinib – 9 Nilotinib – 8 Tretinoin - 3
Eur J Cancer Care. 2018;e12994	Prospective study of oral anti-neoplastic drugs	N=219 patients 736 concomitant medications 34 drug-drug interactions (15.5% of patients) 15 considered to be of little relevance (6.8% of patients)	Nilotinib – 4 Thalidomide - 7
J Oncol Pharm Pract. 2018;24:110	Retrospective review of oral TKI	N=356 patients 224 potential interactions 109 (44.7%) considered severe (30.6% of patients) Most common: PPI (decreased absorption), CYP3A4 Potential consequences: QTc prolongation (48.6%), decreased TKI concentration (48.6%), increased TKI concentration (2.8%)	Dasatinib – 16 Nilotinib – 10 Imatinib – 5 Ibrutinib - 3
BMC Cancer. 2018;18:1155	Retrospective review of patients enrolled on NCTN oncology trials	N=128 Moderate/major DDI based on LexiComp: 24.2% 9.4% clinically relevant based on pharmacist evaluation	Dasatinib – 1 Pomalidomide - 10

Why do interactions reach our patients?



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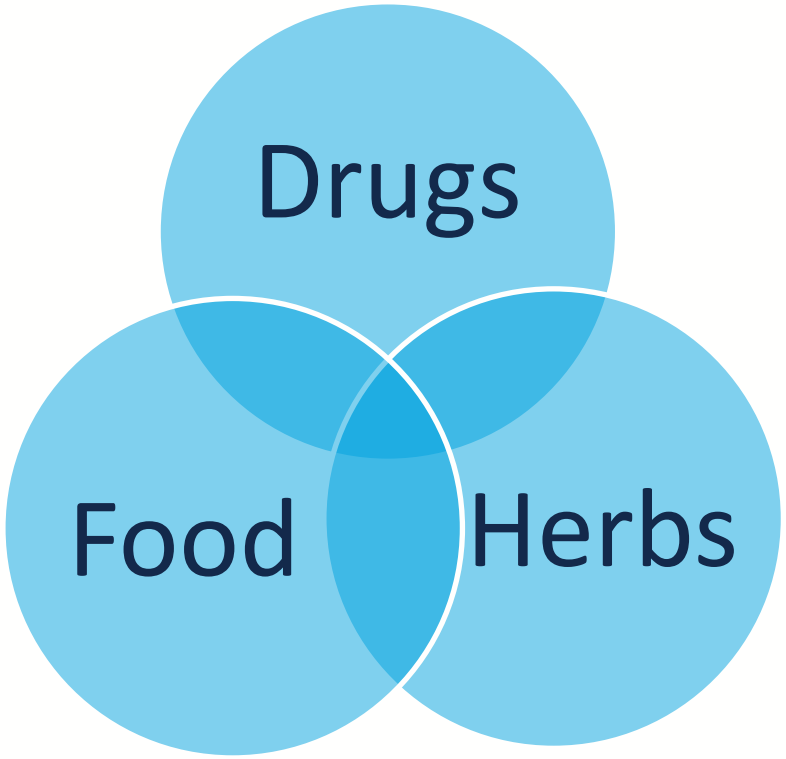
Types of Drug Interactions



Pharmacokinetic

- Absorption/Distribution/Metabolism/Elimination
  - CYP, UGT, PgP, etc.
  - Decreased/increased absorption with food
  - Decreased absorption with drugs

Pharmacodynamic

- Active compounds change each others pharmacologic effect – Synergistic, additive, antagonistic
  - Increased QTc
  - Increased bleeding risk - Ibrutinib

J Oncol Pract. 2019;15:81-90

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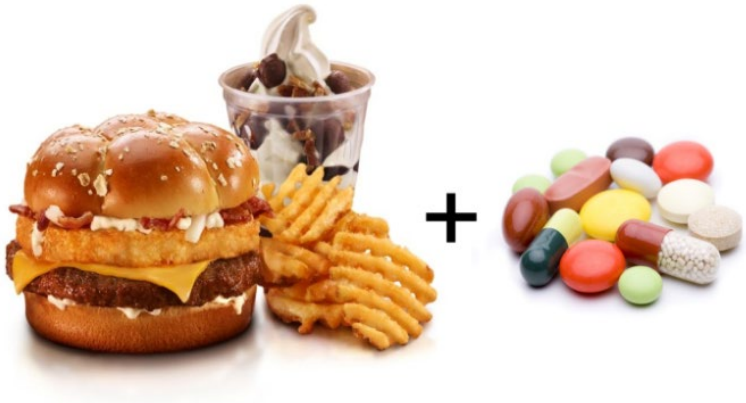
Drug – Food Interactions

- Food increases GI secretions – Decreases gastric pH
  - Increased dissolution and absorption of basic drugs
  - Increased degradation of acid-labile drugs

- High fat meal
  - Decreased gastric empting rates
  - Increased dissolution of fat soluble drugs



- Chelation by polyvalent metal ions

- Grapefruit (pomegranate and star fruit too) – inhibit gut CYP 3A4 and Pgp

Eur J Pharm Sci. 2019; 134:31-59.

Examples of Food Effects on Drug Absorption

	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib	Gilteritinib	Midostaurin	Enasidenib	Ivosidenib	Glasdegib	Venetoclax	Acalabrutinib	Ibrutinib	Zanubrutinib	Duvelisib	Idelalisib	Lenalidomide	Pomalidomide	Thalidomide	Ixazomib	Panobinostat	Selinexor	Vorinostat	Tazemetostat
Take with food	X	X	X*		X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X
Take on empty stomach		X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X		X
High fat meal effects on Cmax	↑ 80%					↓ 26%	↓ 27%		↑ 98%	↓ 31%		↓ 73%	↑ 200-400%		↓ 37%		↓ 50%	↓ 27%	<10%	↓ 69%	↓ 44%		↑ 33%	
High fat meal effects on AUC	↑ 70%	↑ 14%		↑ 82%		↓ 10%	↑ 60%		↑ 25%	↓ 16%	↑ 510%	No effect	↑ 200%		↓ 6%	↓ 40%	↓ 20%	↓ 8%	<10%	↓ 28%	↓ 16%			
High fat meal effects on Tmax							↓ 2h					↓ 1-2h						↓ 2.5h	↓ 6h		↓ 2.5h		↓ 2.5h	

Interaction potential and recommendations based on information included in Prescribing Information for each medication as of 1/2020 (6/2020: selinexor and tazemetostat)

* To decrease gastritis

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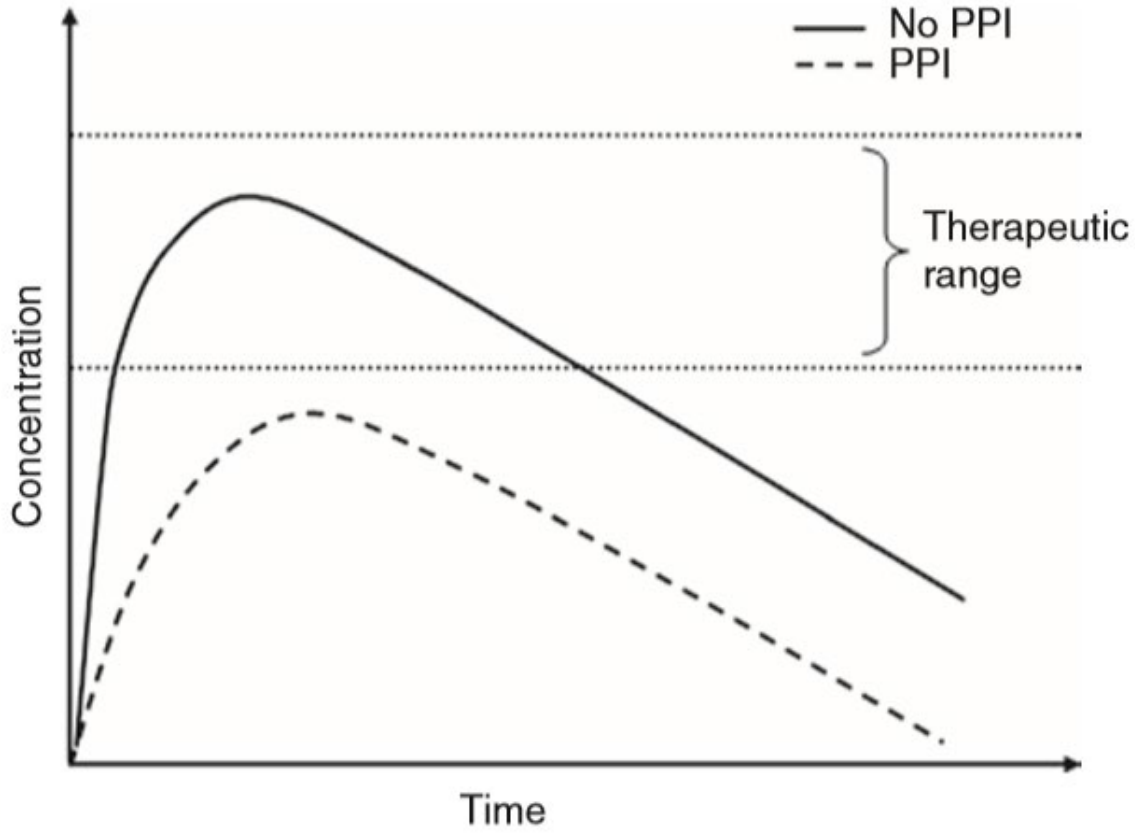
Acid Suppressing Medications and Drug Absorption

Commonly Used Acid-Reducing Agents

Proton pump inhibitors
- Esomeprazole
- Lansoprazole
- Omeprazole
- Pantoprazole
- Rabeprazole

H_2-receptor antagonists
- Cimetidine
- Famotidine
- Nizatidine
- Ranitidine

Other agents
- Antacids, e.g., aluminum hydroxide/carbonate
- Calcium hydroxide/carbonate
- Bismuth subsalicylate
- Buffered medications, e.g., didanosine



Anticipated outcome of interaction between PPI and a targeted agent with pH-dependent solubility.

Clin Pharmacol Ther. 2012;92:203-213

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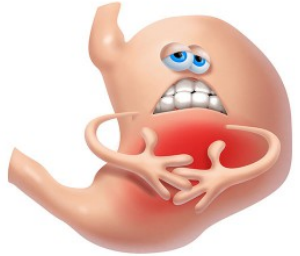
Interactions with Gastric Acid Reducing Medications



	Proton Pump Inhibitors	Histamine 2 Receptor Antagonists	Antacids
Bosutinib	Avoid (AUC ↓ 26%)	Separate dosing by 2 hours	Separate dosing by 2 hours
Dasatinib	Avoid (AUC ↓ 43%)	Avoid (AUC ↓ 61%)	Separate by 2 h (AUC ↓ 55% with concomitant use)
Nilotinib	Avoid (AUC ↓ 34%)	Take 10 h after or 2 h prior H2RA	Separate by 2 h
Acalabrutinib	Avoid (AUC ↓ 43%)	Take 2 h prior to H2RA	Separate by 2 h (AUC ↓ 53% with concomitant use)
Ponatinib	Not significant (AUC ↓ 6%, Cmax ↓ 25%)		
Glasdegib	Not significant (AUC ↓ 0%, Cmax ↓ 20%)		
Tazemetostat	Not Significant (AUC ↓ 26%, Cmax ↓ 25%		

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Interaction potential and recommendations based on information included in Prescribing Information for each medication as of 1/2020 (6/2020 tazemetostat)

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Clinical Impact of Interactions with Gastric Acid Reducing Medications

- Clinical trials lacking

Retrospective review of nilotinib use for CML[1]

Newly diagnosed CML, n=492

- Major molecular response at 12 months: 50% if received at least one PPI or H2RA vs. 41% without co-medication

Imatinib-resistant or –intolerant CML, n=256

- Major cytogenetic response by 12 months: 64% vs. 58%, respectively
- Complete cytogenetic response by 12 months: 45% vs. 38.2%, respectively

- Management:

Avoid use	If PPI unavoidable, use less potent PPI in morning (pantoprazole), 2 hours prior to oral oncolytic	Consider administration with an acidic beverage (cola)[2]

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[1]Cancer Chemother Pharmacol. 2012;70:345-350
[2]J Clin Oncol. 2016;34:1309-14.
Eur J Clin Pharmacol. 2009;65:19-31
Clin Pharmacokinet. 2017;56:683-699

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Interactions in Drug Metabolism

Most commonly via hepatic cytochrome P450 enzymes

- Account for ~75% of drug metabolism[1]

Impact of many transporters may be underappreciated

- Limited number of drugs whose disposition depends on a single transporter
- Drugs are frequently not specific to a single transporter
- Not all combinations of drugs tested for transporter-mediated drug interactions

Intestinal transporters

- P-gp
- Breast cancer resistance protein (BCRP)
- Multidrug resistance protein 2 (MRP2)

Hepatic transporters

- Organic anion transporting polypeptide (OATP)
- Organic cation transporter (OCT)

Renal transporters

- Multidrug and toxin extrusion (MATE), OCT, OAT

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[1]Chem Res Toxicol. 2008;21:70-83
Gessner A, et al. Clin Pharmacol Ther. 2019;105:1386-1394

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Table of Pharmacokinetic Interactions

Enzyme	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib	Gilteritinib	Midostaurin	Enasidenib	Ivosidenib	Glasdegib	Venetoclax	Acalabrutinib	Ibrutinib	Zanubrutinib	Duvelisib	Idelalisib	Lenalidomide	Pomalidomide	Thalidomide	Ixazomib	Panobinostat	Selinexor	Vorinostat	Tazemetostat
CYP 1A2							I/Ind	S/I				Ind						S		S				
CYP 2B6				Ind			Ind	S/I/Ind	Ind			Ind								S				
CYP 2C8				Ind/I	S		I/Ind	S/I	Ind		I	I				I				S				
CYP 2C9							I/Ind	S/I	Ind		I	I								S				
CYP 2C19							Ind	S/I				I		Ind		I		S		S	S/I			
CYP 2D6			I	I	S		I	S/I					S	Ind				S		S	I/S			
CYP 2E1							I																	
CYP 3A	S	S	S/I	S/I	S	S/I	S/I/Ind	S/I/Ind	S/Ind	S	S	S/I/Ind	S	S/Ind	S	S		S		S	S/I	S		S/Ind
P-gp				I	I	S	I	I	S/I	S/I	S/I	S	I	S/Ind	S	S	S	S		S	S			S
UGT 1A1				I				S/I			I					I					S	S		
UGT 1A4								S								S						S		
BCRP					I	I	I	I		S/I	S/I	S/I	I		S	S								
OCT1						I															I			
OCT2								I													I			
OATP 1B1							I	I			S/I										I			
OATP 1B3																						I		
OAT1								I																
OAT3								I	I												I			
BSEP					I																			
MATE 1						Ind				I														I
MATE-2K										I														I

S = Substrate
I = Inhibitor
Ind = Inducer

= avoid inducers
= avoid inhibitors
= avoid substrates
= use substrates with caution

P-gp = P-glycoprotein, BCRP = Breast cancer resistance proteins, OCT = organic cation transporter, OATP = Organic anion transporting polypeptide, OAT = Organic anion transporter, BSEP = Bile salt export pump, MATE = Multidrug and toxin extrusion

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Interaction potential and recommendations based on information included in Prescribing Information for each medication as of 1/2020 (6/2020 selinexor and tazemetotat)

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Recommended Dose Adjustments

Drugs with Dose Adjustments to Manage Interactions in Prescribing Information

Dasatinib	Nilotinib	Ponatinib	Ivosidenib	Venetoclax	Acalabrutinib
Ibrutinib	Duvelisib	Pomalidomide	Panobinostat	Zanubrutinib	Tazemetostat

Example: Venetoclax Dose Adjustment Recommendations

Co-administered Drug	Venetoclax Ramp-Up Phase	Daily Dose (After Ramp-Up Phase)
Posaconazole	CLL/SLL: Contraindicated AML: Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	AML 70 mg
Other strong CYP3A inhibitor	CLL/SLL: Contraindicated AML: Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	AML 100 mg
Moderate CYP3A inhibitor or P-gp inhibitor	Reduce dose by 50%	Reduce dose by 50%

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Venclexta (venetoclax) Prescribing Information. AbbVie, Inc. North Chicago, Il. 11/2018

Pharmacokinetic Interactions with Anticoagulants

Drug	Inhibitors	Inducers
Apixaban	P-gp or strong CYP 3A4 inhibitors: Reduce dose or avoid	P-gp or strong CYP 3A4 inducers: Avoid
Dabigatran	P-gp inhibitor with CrCl 30-50 ml/min: Reduce dose or avoid P-gp inhibitor in patients with CrCl < 30 ml/min: Avoid	P-gp: Avoid
Edoxaban	P-gp: No dose reduction recommended	P-gp inducers: Avoid
Rivaroxaban	P-gp or strong CYP 3A inhibitors: Avoid	P-gp or strong CYP 3A inducers: Avoid
Warfarin	CYP 2C9, 1A2, or 3A4 inhibitors: Reduce dose/increase monitoring or avoid	CYP 2C9, 1A2, or 3A4 inducers: Reduce dose/increase monitoring or avoid
Low Molecular Weight Heparin	No Interactions	No Interactions

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Interaction potential and recommendations based on information included in Prescribing Information for each medication as of 1/2020

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Ibrutinib-induced Atrial Fibrillation

- Ibrutinib: 16% incidence of atrial fibrillation
- Commonly used treatments have significant interactions
  - CYP3A4, PgP
- Pharmacodynamic interactions
  - Inhibits platelet signaling and aggregation
  - 55% experience grade 2 or less bleeding over 24 month period[1]

Fish oil	Aspirin	NSAIDs	Anticoagulants	Vitamin E

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[1]Haematologica. 2015;100:1571-78.

J Thromb Haemost. 2017;15:835-47.

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Ibrutinib-induced Atrial Fibrillation

- Recommendations:
  - Rate control: Metoprolol
  - Antiplatelet stroke prevention: None recommended due to increased bleeding risk
  - Warfarin: Not recommended
  - Direct oral anticoagulants:
    - Least potential for interaction: apixaban, dabigatran and edoxaban
  - Avoid antiplatelet agents, vitamin E, and fish oil

- Acalabrutinib and zanubrutinib not associated with platelet effects

Agents	CYP 3A4	P-glycoprotein	Potential Impact on Ibrutinib Conc.	Potential Impact on Cardiac Medication Conc.	Pharmacodynamic* Interaction	Co-Administer
Ibrutinib	**S**	**INH**				
Rate Control Agents						
Metoprolol						Y
Verapamil	S, INH	INH	↑			N
Diltiazem	S, INH		↑[+]			N
Digoxin	S	S		±/↑		N
Rhythm Control Agents						
Flecainide						Y
Propafenone	S	INH				?
Sotalol						Y
Dofetilide	S					?
Dronedarone	S, INH	INH	↑			N
Amiodarone	S, INH	S, INH	↑	↑		N
Stroke Prevention Agents						
Dabigatran		S		↑	X	?
Rivaroxaban	S	S		±/↑	X	?
Apixaban	S	S		±/↑	X	?
Edoxaban		S		↑	X	?
Betrixaban		S		↑	X	?
Warfarin	S			±	X	?
Antiplatelet Agents						
Clopidogrel					X	N
Prasugrel					X	N
Ticagrelor	S	INH			X	N
Aspirin						N

*Footnotes: Conc: Concentrations; **INH:** Inhibitor; **S**: substrate; ↑: Increase; ↓: Decrease; **±:** Effect unknown of potential impact of competition for metabolism by CYP 3A4 among drugs with a narrow therapeutic index.*
**Additive bleeding risk*
[+]Combination of diltiazem and ibrutinib contraindicated

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Rao VU, Buck M, Reeves D, Skurka K, Rubenstein S. Clinical Challenges Associated with Management of Ibrutinib-induced Atrial Fibrillation. Global Cardio Oncology Summit 2018. Sept 2018

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QT Prolongation

- Risk with targeted therapies: 0 - 5.2%[1]
- Arrhythmia/sudden cardiac death as a result of QT prolongation is rare: 0.1%[2]
- Risk factors
  - Electrolyte disturbances (mucositis, emesis, diarrhea, decreased intake)

Strategies to Minimize Cancer Therapy Related QTc Prolongation
Avoid QTc-prolonging drugs if pretreatment QTc >450 ms
Discontinue QTc-prolonging drug(s) if QTc prolongs to >500 or >550 ms if baseline widening of QRS
Reduce dose or discontinue QTc-prolonging drug(s) if QTc increases ≥60 ms from baseline
Maintain potassium, magnesium, and calcium within normal range
Avoid drug interactions
Adjust doses appropriately in patients with kidney dysfunction
Avoid rapid IV administration of QTc-prolonging drugs
Avoid administration of >1 QTc prolonging drug
Avoid QTc-prolonging drugs in patients with a history of TdP or resuscitation after sudden cardiac death
Avoid use of QTc–prolonging drugs in patients with congenital long QT syndromes
Monitor ECG

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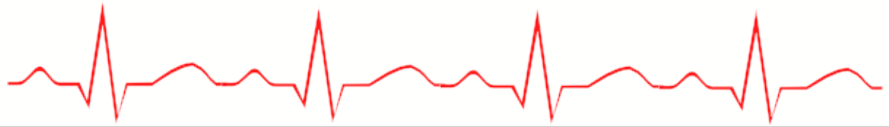
J Am Heart Assoc. 2017;6:e007724.
J Oncol Pract. 2019;15:81-90.

QTc Monitoring Recommendations



Drug	Baseline QTc Monitoring	QTc Monitoring During Treatment
HDAC Inhibitor		
Panobinostat	ECG	ECG q 3 weeks x 8
Vorinostat	ECG	If patient at risk or receiving QT prolonging medications: ECG 2 weeks after drug initiation and at 1 and 3 months*
BTK Inhibitor		
Acalabrutinib		A. Fib: ECG in patients who develop palpitations, lightheadedness, syncope, or chest pain
Ibrutinib		A. Fib: ECG in patients who develop palpitations, lightheadedness, syncope, or chest pain
Zanubrutinib		A. Fib: ECG in patients who develop palpitations, lightheadedness, syncope, or chest pain
BCR-ABL Inhibitor		
Bositinib	ECG	ECG q 4 weeks x 3
Dasatinib	ECG	ECG at week 4
Nilotinib	ECG	ECG on day 8 then every 3 cycles x 3
Ponatinib	ECG	ECG week 4
FLT 3 Inhibitor		
Midostaurin	ECG	In patient at risk or receiving QT prolonging medications: ECG on day 3 and 14 of midostaurin during induction and consolidation cycles then every other cycle during continuation therapy
Gilteritinib	ECG	ECG on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles
IDH1 Inhibitor		
Ivosidenib	ECG	ECG weekly x 3 then monthly
Hedgehog Pathway Inhibitor		
Glasdegib	ECG	ECG at week 2 then monthly x 2

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Recommendations based on QT prolongation risk and recommended monitoring included in Prescribing Information for each medication

Journal of Oncology Practice®
An American Society of Clinical Oncology Journal

Potential Drug-Drug and Herb-Drug Interactions in Patients With Cancer: A Prospective Study of Medication Surveillance

- N=149
- 56.4% reported using concurrent herbal supplements
- 122 possible interactions detected

Table 3. Potential HDIs Found in Data Set

Herbal Supplement	Mechanism of Interaction	Anticancer Agent Involved (No. of patients)
Allium sativum	Inhibits CYP3A4 and 2C9 Induces P-glycoprotein synthesis	Paclitaxel (8), irinotecan (4), abiraterone acetate (2), cyclophosphamide (2)
Aloe barbadensis/capensis	Decreases intestinal absorption Inhibits CYP3A4	Tamoxifen (8), capecitabine (6), cyclophosphamide (6), paclitaxel (6), abiraterone acetate (2), irinotecan (2) anastrozole (2), imatinib (2), vincristine (1), vinorelbine (1), erlotinib (1)
Annona muricata	Inhibits P-glycoprotein	Paclitaxel (3)
Camelia sinesis	Inhibits P-glycoprotein and CYP3A4 Increases bioavailability of tamoxifen	Paclitaxel (4), abiraterone acetate (2), cyclophosphamide (2), tamoxifen (1), irinotecan (1)
Ecchinacea angustfolia	Inhibits CYP3A4	Sorafenib (1), erlotinib (1)
Gingo biloba	Inhibits CYP2C9 and 1A2 Induces CYP1A2	Anastrozole (4)
Matricata recutita	Inhibits CYP2D6, 3A4, and 2C9	Tamoxifen (1)
Moringa oleifera	Inhibits CYP3A4	Cyclophosphamide (3), docetaxel (1)
Panax ginseng	Induces CYP3A4	Abiraterone acetate (1), sorafenib (1), cyclophosphamide (1), docetaxel (1)
Spirulina sp.	Inhibits CYP1A2	Anastrozole (1)
Uncaria tomentosa	Inhibits CYP3A4	Abiraterone acetate (2), paclitaxel (1)
Valeriana officinalis	Inhibits CYP2D6 Induces CYP3A4	Tamoxifen (4), paclitaxel (4)
Vitis vinifera	Inhibits CYP3A4 and 2C9	Paclitaxel (9), cyclophosphamide (8), vincristine (1), tamoxifen (3), anastrozole (3), abiraterone acetate (2), exemestane (1), irinotecan (1), imatinib (1)

Abbreviations: HDI, herb-drug interaction; P-glycoprotein, phosphoglycoprotein.

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J Oncol Pract. 2017;13:443

What about CBD oil?

- FDA approved formulation available for seizure treatment: Epidiolex
- Inhibits CYP 2C8, 2C9, 2C19
- May inhibit or induce CYP 1A2, 2B6
- Inhibits UGT 1A9, 2B7
- May inhibit BCRP and BSEP

- Unknown impact of impurities: up to 70% of products tested positive for heavy metals (i.e., lead, arsenic), pesticides, mold, other impurities

Prescribing Information Epidiolex (cannabidiol). Greenwich Biosciences, Inc. Carlsbad CA. 06/2018

The risk of contaminants and false labeling in the exploding CBD industry. WJLA/ABC7, May 2019. https://wjla.com/features/7-on-your-side/the-risk-of-contaminants-and-false-labeling-in-the-exploding-cbd-industry (Accessed 1/20/2020)

Management Strategies – Identifying Interactions

Drug-Drug Interaction Databases

- Lexicomp/LexiInteract, MicroMedex, ClinPharm, Epocrates, Drugs.com

Herb-Drug Databases

- Natural Medicines Comprehensive Database: https://naturalmedicines.therapeuticresearch.com/
- Memorial Sloan Kettering Cancer Center – About Herbs, Botanicals & Other Products: https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs

Sensitivities of detecting known interactions with oncologic medications[1]

- Micromedex: 70%
- Facts & Comparisons: 70%
- Epocrates: 90%
- Lexi-Interact: 95%
- Drugs.com: 95%

- Only 3 of 20 interactions were classified at the same level of severity in all databases

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[1]J Oncol Pract. 2017;13:e217-e222

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Management Strategies - Reacting

Determination of need to continue interacting medications

Alternative therapy

Dose adjustments

Increased monitoring

- Adverse effects
- ECG monitoring

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Managing Drug Interactions with Oral Oncolytics in the Management of Hematologic Malignancies

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