Recognizing Toxicites of Oral Oncolytics in the Management of Hematologic Malignancies

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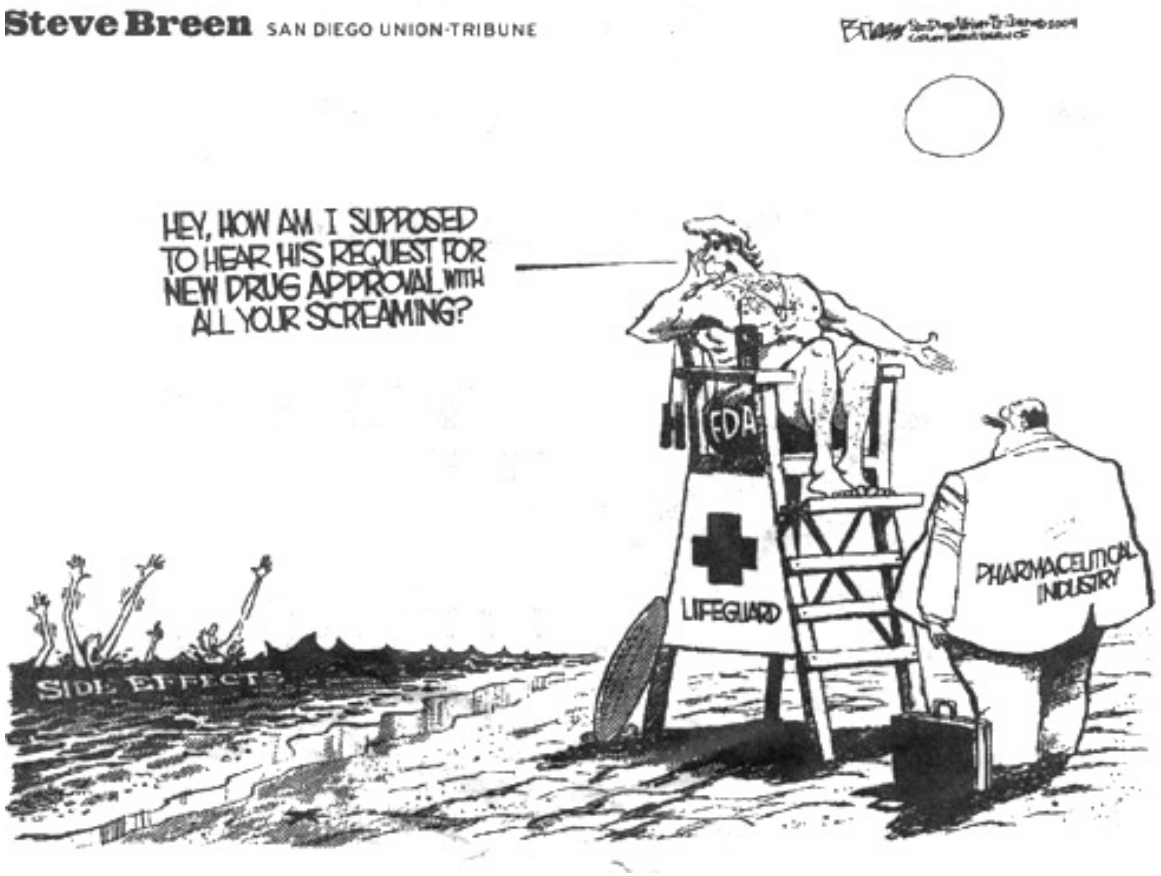
Objectives & Disclosure

Identify common adverse effects associated with oral oncolytic therapies utilized to treat hematologic malignancies

Propose a strategy to manage a patient experiencing an adverse effect while receiving an oral oncolytic agent



Disclosure

- *I have no conflicts of interest to disclose*
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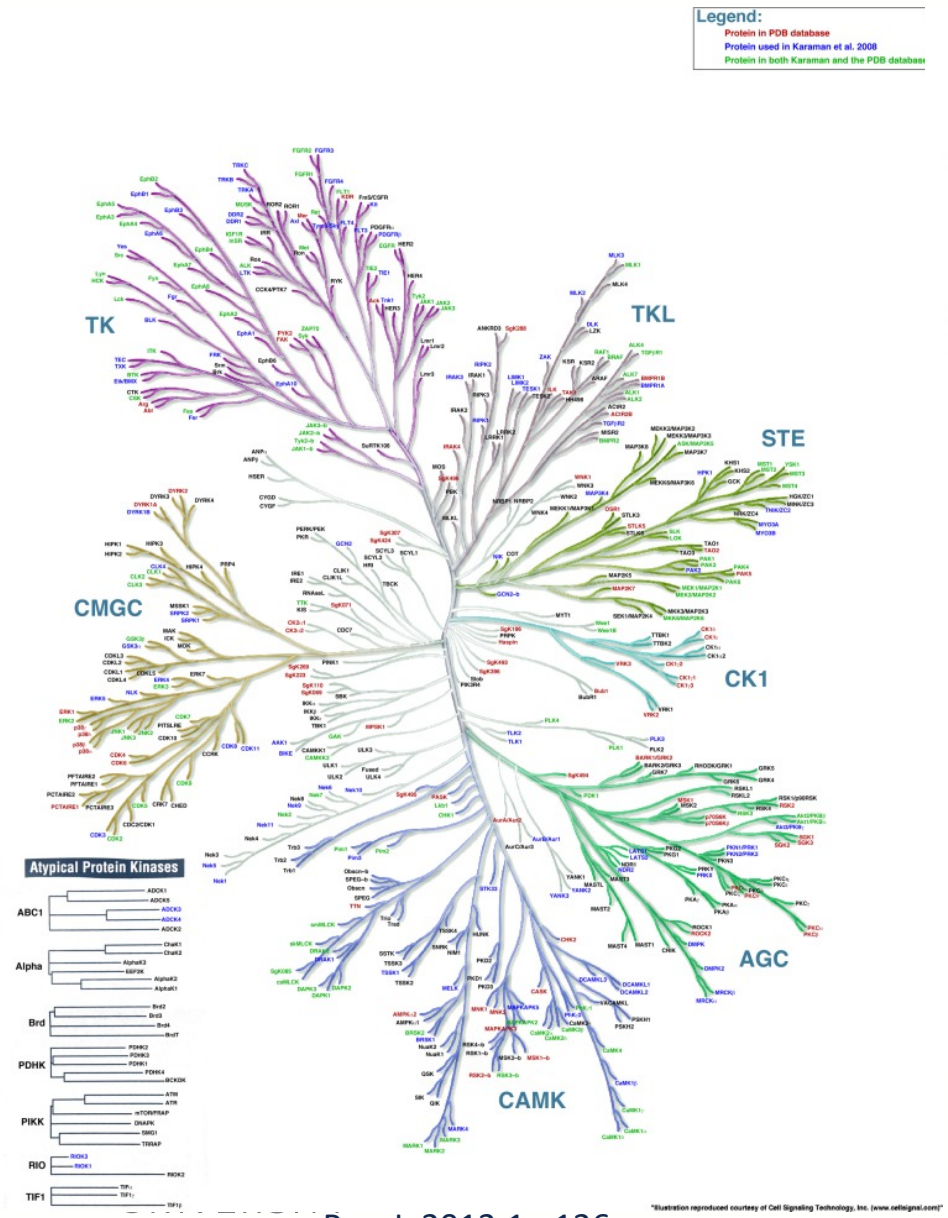
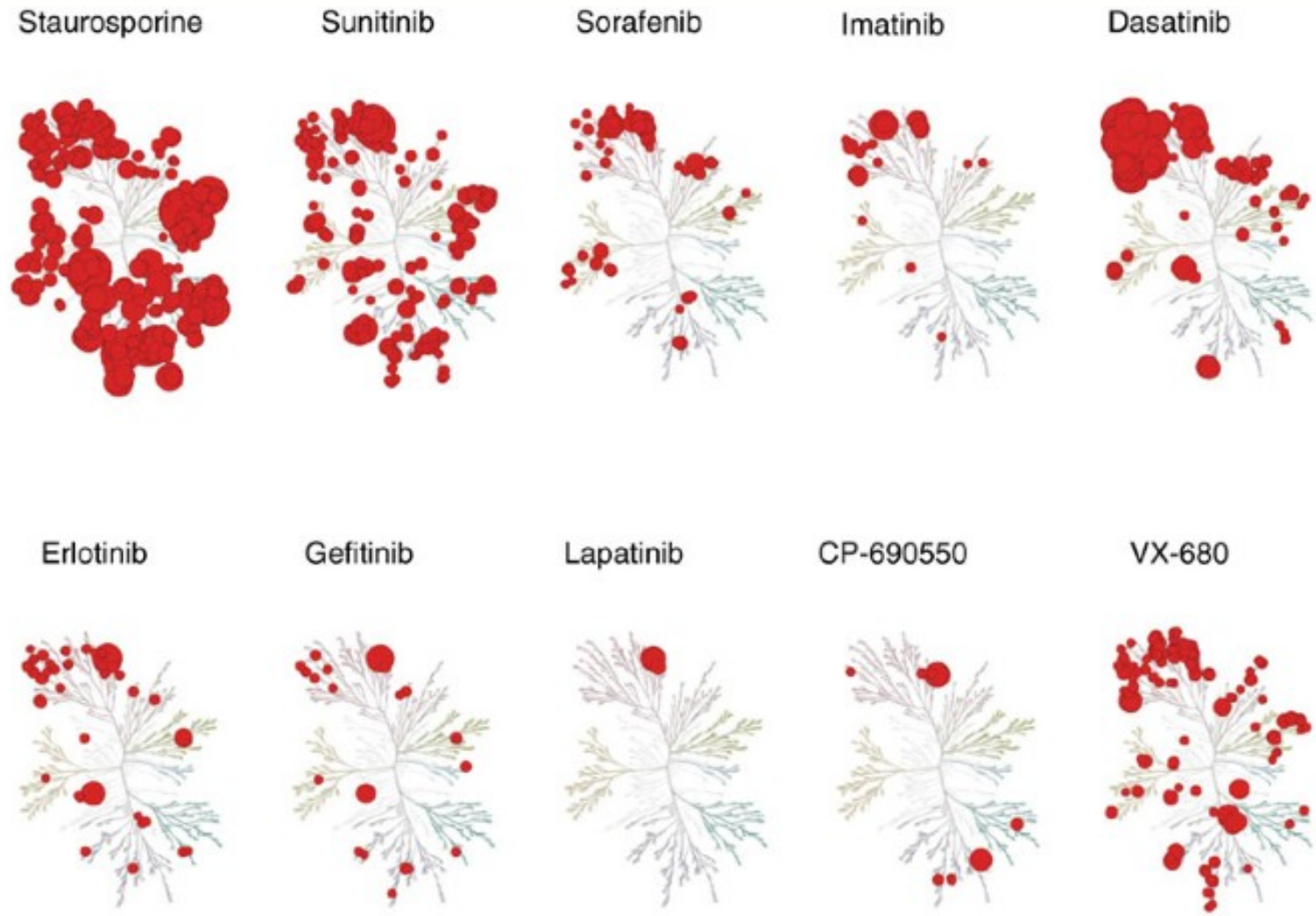
Common Toxicities

Nausea/Vomiting	Diarrhea	Rash/Dermatologic toxicities	Cardiac toxicities
Infection	Myelosuppression	Hepatotoxicity	Electrolyte abnormalities
Fatigue	Hypothyroidism	Pneumonitis	Tumor lysis syndrome

Human Kinome



PeerJ. 2013;1:e126.



Nature Immunology. 2009;10:356-60.

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Impact of Oral Oncolytic Toxicity

Eight oncology practices in Michigan

- Investigation of patient-reported outcomes
- Evaluate symptom burden of patients prescribed oral oncolytics before each outpatient visit

1,235 ESAS-r surveys collected

- Symptoms categorized as mild, moderate or severe

Symptom	ESAS-r Symptom Score (%)		
	Mild (0-3)	Moderate (4-6)	Severe (7-10)
Pain	80	15	5
Tiredness	65	21	14
Drowsiness	75	16	9
Nausea	92	6	2
Appetite	79	13	8
Shortness of Breath	87	9	3
Depression	86	11	3
Anxiety	87	10	3
Well-being	66	21	13
Constipation	87	10	3
Diarrhea	92	5	3
Tingling/numbness	81	12	6
Mouth sores	96	3	1

ESA-r: revised Edmonton Symptom Assessment System

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J Oncol Pract. 2017;13:e395-400

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2018 Hematology/Oncology Pharmacist Association Best Practices for the Management of Oral Oncoloytic Therapy: Pharmacy Practice Standard

Education

- Education should be comprehensive and focus on patient self-care management of oral oncolytic adverse effects and the importance of medication adherence
- An assessment of patient knowledge, confidence to manage adverse effects and need for follow-up should occur during the education session

Monitoring and follow-up

- Initial monitoring of symptoms and adherence, including PROs, should occur between 7 and 14 days after the start to treatment
- Ongoing monitoring of symptoms and adherence, including PROs, should occur at each clinical encounter, at least before each refill

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J Oncol Pract 2018:15;e346-e355

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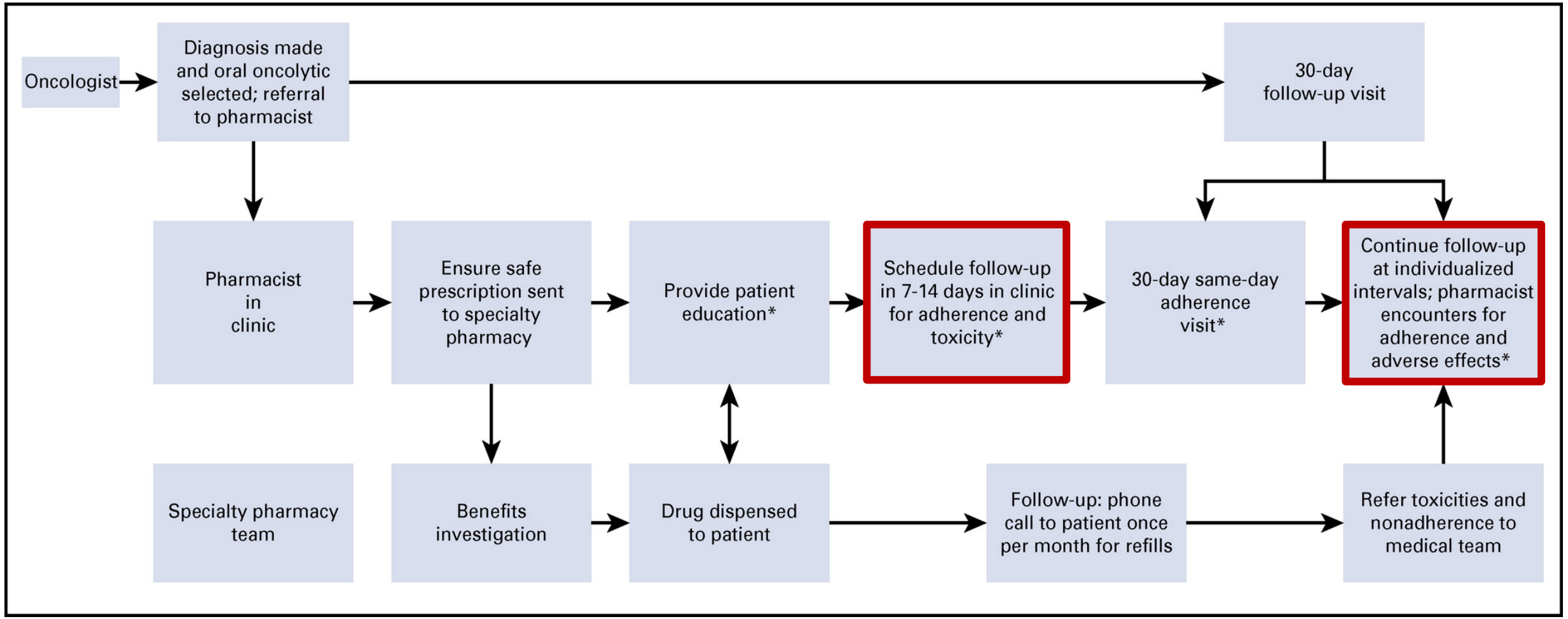
2018 Hematology/Oncology Pharmacist Association Best Practices for the Management of Oral Oncoloytic Therapy: Pharmacy Practice Standard



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J Oncol Pract 2018;15:e346-e355

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Emetogenic Potential of Oral Oncolytics

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Antiemesis

Level	Agent		
Moderate to high emetic risk (≥ 30% frequency of emesis)	Azacitidine Bosutinib > 400 mg/day Enasidenib	Fedratinib Imatinib > 400 mg/day Midostaurin	Selinexor
Minimal to low emetic risk (< 30% frequency of emesis	Acalabrutinib Bosutinib ≤ 400 mg/day Chlorambucil Dasatinib Decitabine/cedazuridine Duvelisib Gilteritinib Glasdegib Ibrutinib	Idelalisib Imatinib ≤ 400 mg/day Ivosidenib Ixazomib Lenalidomide Nilotinib Panobinostat Pomalidomide Ponatinib	Tazemetostat Thalidomide Tretinoin Umbralisib Venetoclax Vorinostat Zanubrutinib

Prevention and Management of Nausea and Vomiting

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Antiemesis

High to Moderate Emetic Risk → Start before anticancer therapy and continue daily:

5-HT3 RA (i.e., ondansetron 8-16 mg/day) + PRN agent for breakthrough nausea/vomiting

Low to Minimal Emetic Risk → PRN recommended → Nausea/ Vomiting → Start before anticancer therapy and one of the below daily:

Metocolpramide 10 – 20 mg PO and then every 6 hours PRN
Prochloperazine 10 mg PO and then every 6 hours PRN
5-HT3 RA (i.e., Ondansetron 8-16 mg PO daily PRN

***Consider and check for drug-drug interactions**

Selinexor: Integrated safety profile of selinexor in multiple myeloma

N=437 patients enrolled in clinical trials

Nausea: 68%

- Grade 3: 6%

Vomiting: 37%

Median time to N/V: 3 days

- Time to grade 3 N/V: 16 days

Duration of N/V

- 22 days if no supportive care within 5 days
- 13 days if supportive care within 5 days

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Leukemia. 2020;34:2430–2440

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Selinexor: Integrated safety profile of selinexor in multiple myeloma

Most patients received 5HT3 antagonist on day of and day after dosing

- Other agents improved control: rolapitant, aprepitant, fosaprepitant, lorazepam, dronabinol, and olanzapine

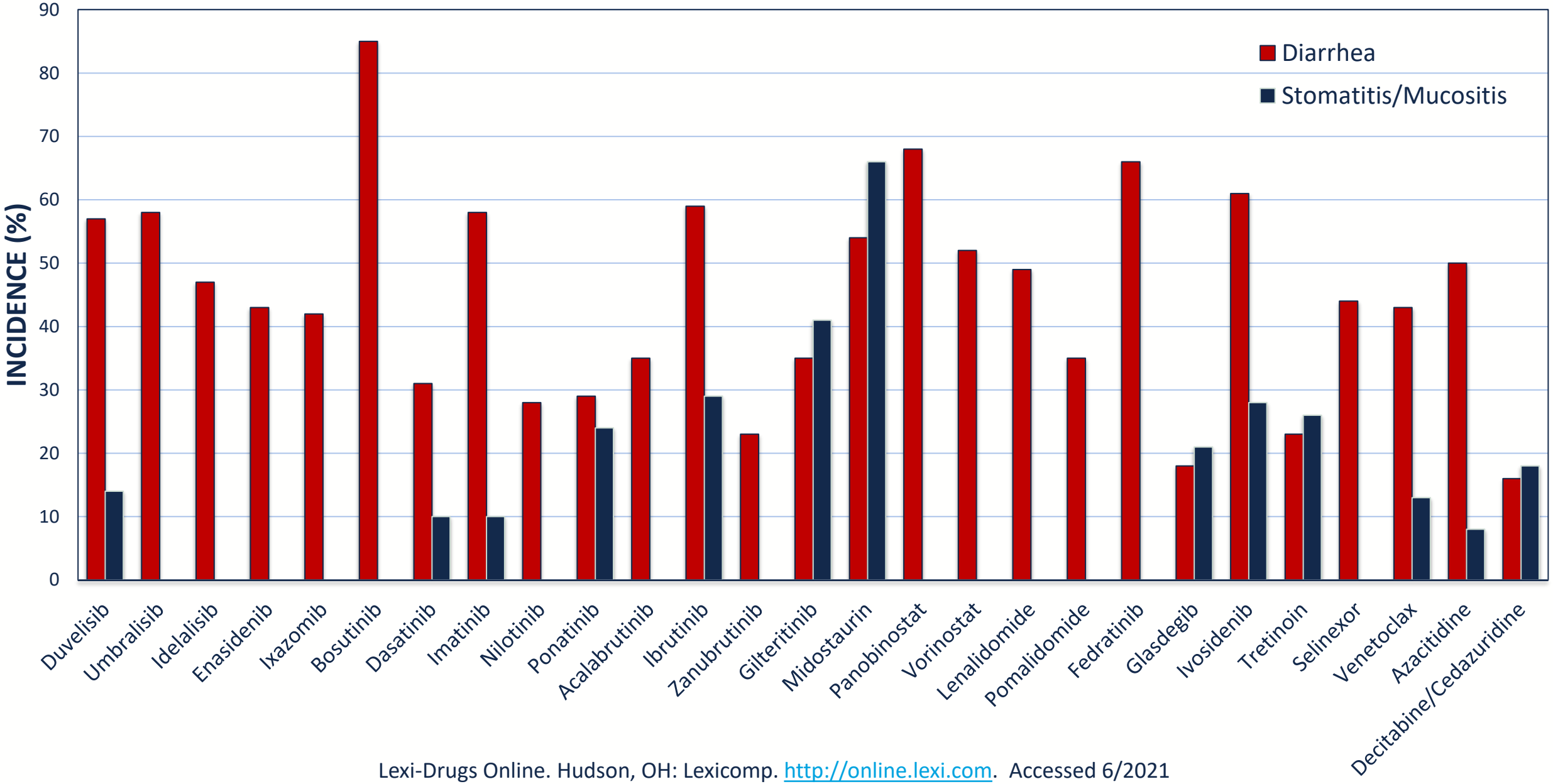
Incidence and severity of decreased appetite at the time of supportive care with outcomes of patients who had intervention within 5 days of AE onset

	No Supportive Care	Serotonin Receptor Antagonist	Dopamine (D2/D3) Receptor Antagonist	NK1 Antagonist	Benzo-diazepine	Steroid	Cannabinoid Receptor Agonist	Histamine (H1) Receptor Agonist	Olanzapine
Patients with any grade nausea/ vomiting (%)	69	38	54	8	8	12	3	6	4
AEs resolved/resolving (%)	56	59	65	72	69	36	90	56	77
Median duration of event for resolved/resolving nausea/vomiting (days)	22	8	7	9	6	13	12	11	15

Supportive care agents per drug class: cannabinoid receptor agonist (dronabinol, nabilone, cannabis sativa, steroid (dexamethasone, prednisolone, prednisone)

Leukemia. 2020;34:2430–2440

GI Toxicities



Lexi-Drugs Online. Hudson, OH: Lexicomp. http://online.lexi.com. Accessed 6/2021

GI Toxicities: Grading

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea (A disorder characterized by an increase in frequency and/or loose or watery bowel movements)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Oral Mucositis (A disorder characterized by ulceration or inflammation of the oral mucosa)	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

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Common Terminology Critera for Adverse Events (CTCAE) Version 5.0; 2017. https://ctep.cancer.gov

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GI Toxicities: Clinical Pearls

Diarrhea

- First line therapy: Loperamide
  - May be more effective than diphenoxylate/atropine
- Refractory grade 1 or 2 or grade 3 or 4 diarrhea: consider SQ octreotide
  - Long acting octreotide may take 10 days to reach therapeutic levels

Stomatitis/Mucositis

- Educate on good oral hygiene
- Lidocaine based mouthwashes common – limited evidence to support
- Zinc supplements may help prevent oral mucositis
- Glutamine powder (10g/d) PO may be beneficial in preventing mucositis
- Doxepin 0.5% mouthwash may be effective to treat pain

Medication	Suggested Dosing Guidelines
Loperamide	4 mg orally initially, then 2 mg q4 hours or after every unformed stool; can increase to 2 mg q2 hours if needed
Deodorized tincture of opium (10 mg/mL)	10-15 drops in water q3-4 hours
Atropine	0.25-1 mg IV or SC
Diphenoxylate/atropine	1-2 tabs by mouth q6-8 hours
Octreotide	100-150 mcg SC 3x daily, or 25-50 mcg/hr by continuous infusion
Budesonide	9 mg by mouth daily, or 3 mg by mouth 3x daily
Glutamine	0.3 mg/kg IV daily, or 20 g by mouth daily
Celecoxib	400 mg by mouth twice daily
Octreotide LAR	30-40 mg SC q28 days
Probiotics	1-2 x 10^{10} by mouth twice daily
Kampo Medicine	7.5 mg by mouth 3x daily

J Hematol Oncol Pharm. 2012;2:143-51.
Cancer. 2014;120:1453-61.
Nutr Clin Pract. 2016;31:171-9.

Cardiac Toxicities

+ = Rare; incidence of adverse effect < 1%
++ = Uncommon; incidence of adverse effect 1-10%
+++ = Frequent; incidence of adverse effect > 10%

Drug	QT Prolongation	Hypertension	Bradycardia	Tachycardia	Atrial Fibrillation	Left Ventricular Dysfunction	Other
Bosutinib (Bosulif)	+					++	
Dasatinib (Sprycel)	++					++	PAH: ++
Imatinib (Gleevec)		+				++	PAH: +
Nilotinib (Tasigna)	+						MI*/VAT: +++
Ponatinib (Iclusig)	+	+++	+	+	++	+++	MI*/VAT: +++
Acalabrutinib (Calquence)					++		
Ibrutinib (Imbruvica)		+++			+++		Ventricular Arrhythmia: +
Zanubrutinib (Brukinsa)					++		
Gilteritinib (Xospata)	++						
Midostaurin (Rydapt)	++						
Panobinostat (Farydak)	++						MI: ++
Vorinostat (Zolinza)	++						VAT: ++
Lenalidomide (Revlimid)						++	VAT: +++
Pomalidomide (Pomalyst)						+	VAT: ++
Thalidomide (Thalomid)		+++	+			+	VAT/MI: +++
Fedratinib (Inrebic)						++	
Glasdegib (Daurismo)	++						
Ivosidenib (Tibsovo)	++						
Tretinoin (Vesanoid)		+++	+++			++	VAT: ++

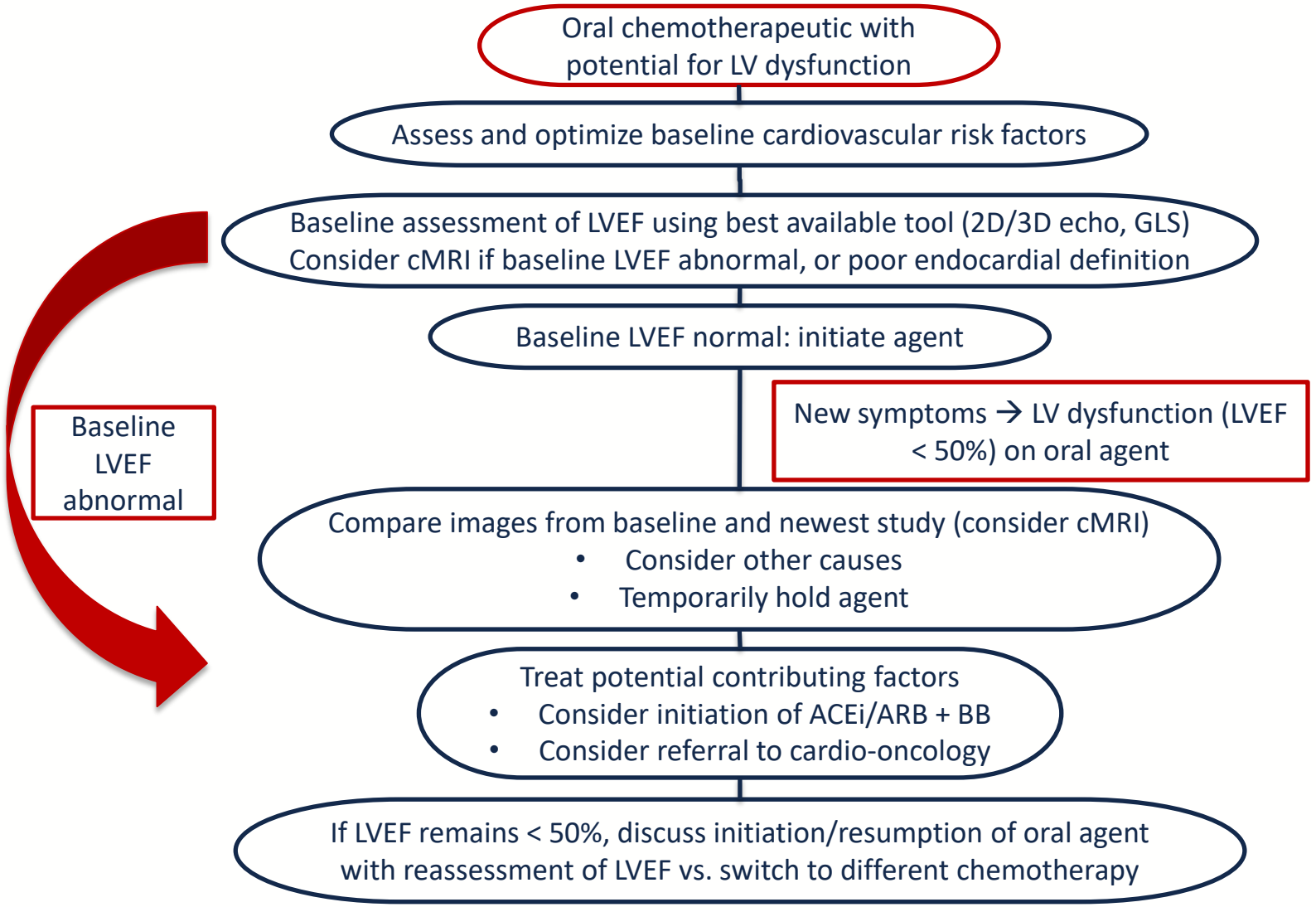
J Am Coll Cardiol. 2021;77:2693–2716

Cardiac Toxicities: Monitoring Recommendations

Drug Target	Drug	Baseline Cardiac Monitoring
BCR-ABL	Bosutinib (Bosulif)	ECG, LVEF
	Dasatinib (Sprycel)	ECG, LVEF
	Imatinib (Gleevec)	BP, LVEF
	Nilotinib (Tasigna)	ECG, Fasting lipid panel
	Ponatinib (Iclusig)	HR/BP, ECG, LVEF, Fasting lipid panel
BTK	Acalabrutinib (Calquence)	ECG
	Ibrutinib (Imbruvica)	BP, ECG
	Zanubrutinib (Brukinsa)	ECG
FLT3	Gilteritinib (Xospata)	ECG
	Midostaurin (Rydapt)	ECG
HDAC	Panobinostat (Farydak)	ECG
	Vorinostat (Zolinza)	ECG
Immunomodulators	Lenalidomide (Revlimid)	LVEF
	Pomalidomide (Pomalyst)	LVEF
	Thalidomide (Thalomid)	HR/BP, LVEF
Miscellaneous Therapies	Fedratinib (Inrebic)	LVEF
	Glasdegib (Daurismo)	ECG
	Ivosidenib (Tibsovo)	ECG
	Tretinoin (Vesanoid)	HR/BP, LVEF

J Am Coll Cardiol. 2021;77:2693–2716

Management of Heart Failure



Clinical Pearls
Obtain baseline LVEF with best available technique before initiation of cardiotoxic oral therapy. Repeat imaging using the same modality with new symptoms or change in clinical status. Study images should be reviewed and compared with baseline images to ensure that LVEF variations are truly present.
Consider CMR if discrepancies in sequential LVEF are present, borderline LVEF is noted, or echocardiogram imaging windows are poor.
When LV dysfunction is noted (at baseline or after initiation of therapy), recommend ruling out ischemic and reversible non-ischemic causes.
ACE inhibitor/ARB/BB should be initiated in the setting of LV dysfunction with oral agents.
Multidisciplinary approach is essential when LV dysfunction occurs, weighing the risk versus benefit of continuing with oral chemotherapy.

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J Am Coll Cardiol. 2021;77:2693–2716

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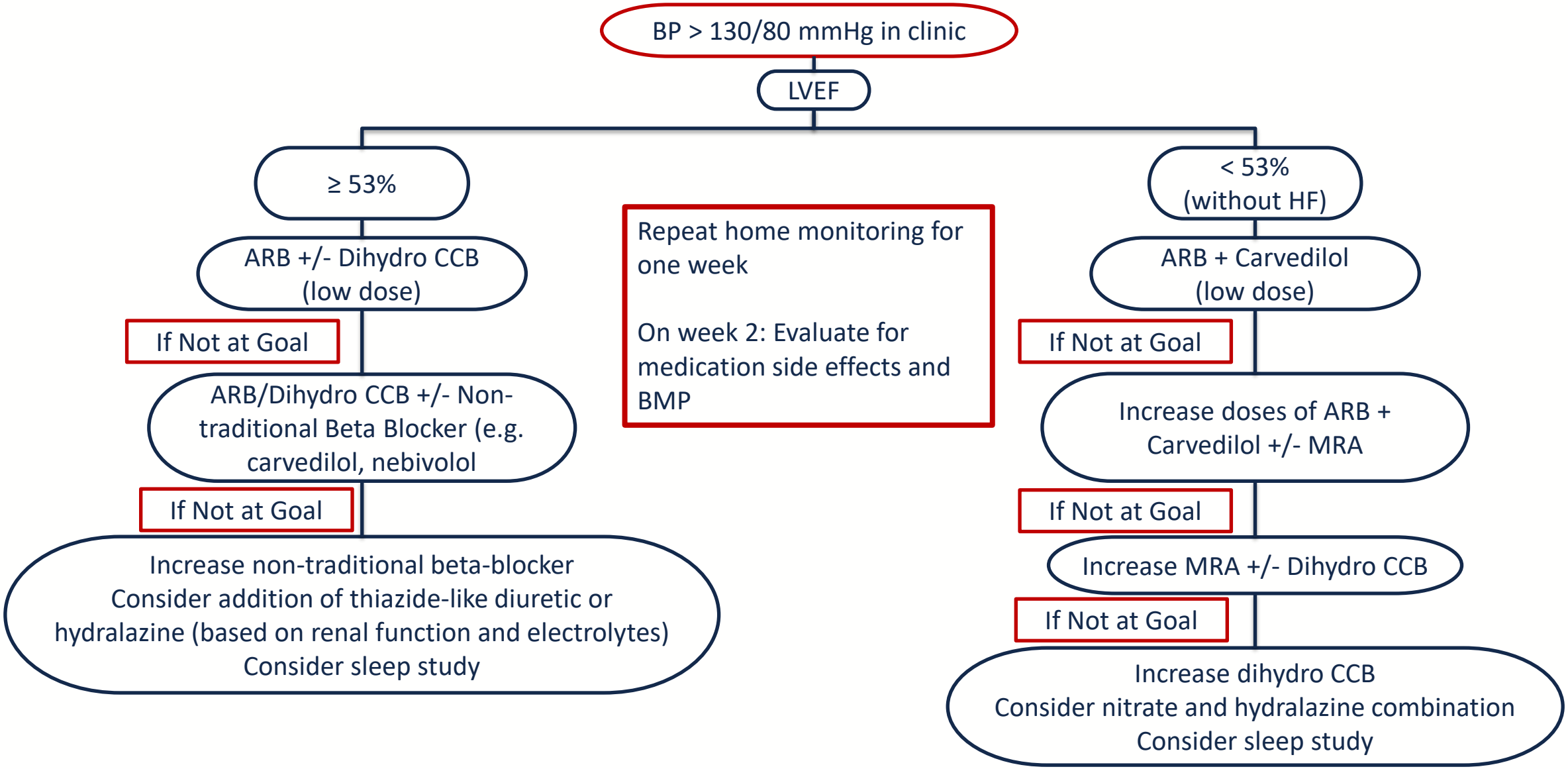
Management of Hypertension



J Am Coll Cardiol. 2021;77:2693–2716

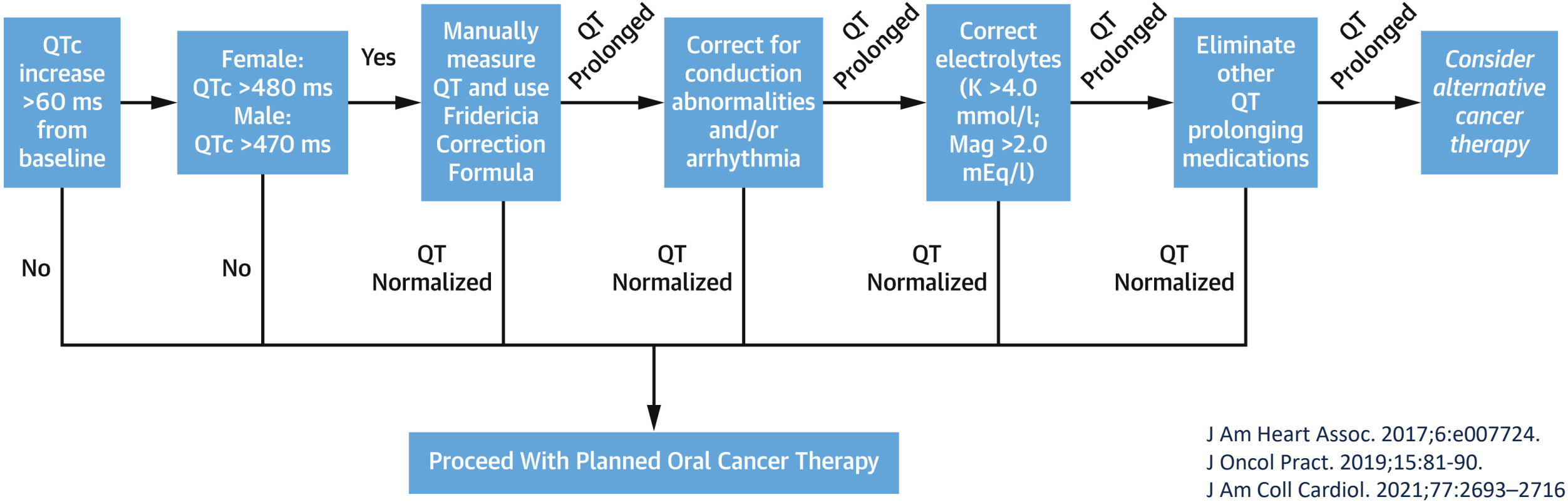
QT Prolongation

Risk with targeted therapies: 0 - 5.2%[1]

Arrhythmia/sudden cardiac death as a result of QT prolongation is rare: 0.1%[2]

Risk factor: Electrolyte disturbances (mucositis, emesis, diarrhea, decreased intake)

Algorithm for QT-Interval Monitoring in Patients Receiving Oral Antineoplastic Agents



J Am Heart Assoc. 2017;6:e007724.
J Oncol Pract. 2019;15:81-90.
J Am Coll Cardiol. 2021;77:2693–2716

BTK Induced Atrial Fibrillation

- Incidence: 6-9%
- Increased bleeding risk (3-5%)
- Bleeding and drug interactions complicate AF therapy

Table 3 Recommendation Summary for Anticoagulant Use in Ibrutinib-Related Atrial Fibrillation

Antithrombotic therapy	Initial dosing recommendations[a]	Maintenance dose
Apixaban	2.5 mg twice daily	5 mg twice daily
Rivaroxaban	15 mg once daily, with food	20 mg once daily, with food
Edoxaban	30 mg once daily	60 mg once daily
Dabigatran[b]	110 mg twice daily	150 mg twice daily
Warfarin	Use may be discouraged, because of increased risk for bleeding	
LMWH	Use may be discouraged, because of lack of long-term safety/efficacy data in patients with ibrutinib-related AF	
Aspirin	May be considered in patients unable to use direct oral anticoagulants or warfarin with low thrombotic risks	

Consider for 1st 7-10 days if HAS-BLED >3

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	?

JHOP. 2019;9:47-50.
Hematol Oncol. 2018;36:624-32.
Rao VU, et al. Clinical Challenges Associated with Management of Ibrutinib-induced Atrial Fibrillation. Global Cardio Oncology Summit 2018. Sept 2018

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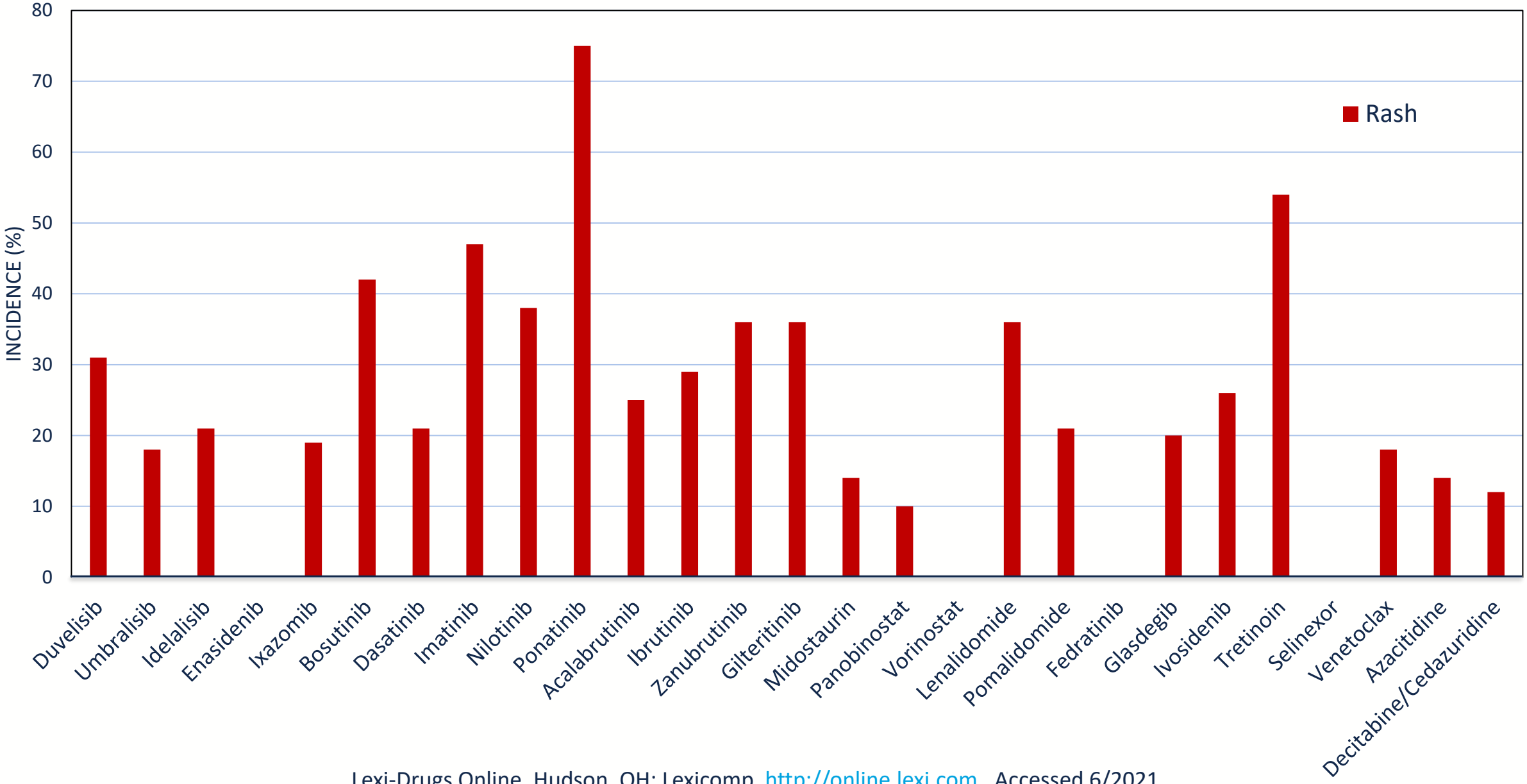
Rash



Lexi-Drugs Online. Hudson, OH: Lexicomp. http://online.lexi.com. Accessed 6/2021

Rash Management

Assess possible causes of rash, e.g., contact with inflammatory substances, allergies, side effect of other

Encourage adequate hydration (daily fluid intake of ≥ 2–3 l) to assist in the maintenance of healthy skin

Promote basic skin care, encourage patients to avoid factors that cause skin irritation, use pH-neutral soaps, and wear loose-fitting, lightweight cotton clothes

Some mild rashes may be managed with antihistamines and topical treatments

If a clinically significant moderate or severe rash develops, consider consultation with a dermatologist for the use of topical or systemic medical treatments

Follow FDA approved labeling for recommendations regarding withholding, dose reductions, or discontinuation

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J Hematol Oncol. 2018;11:143

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Infectious Complications

Myelosuppression common with most agents

Hepatitis B reactivation

- 2020 testing update: recommended for all patients anticipating systemic anticancer therapy
  - Hepatitis B surface antigen
  - Hepatitis B surface antibody
  - Hepatitis B core antibody
- Anticancer therapy should not be delayed

Prophylaxis recommended for some agents

- Ixazomib: acyclovir during treatment
- PIK3 inhibitors (duvelisib, idelalisib, umbralisib): PJP prophylaxis
  - Trimethoprim/sulfamethoxazole, dapsone, pentamidine, or atovaquone
- BTK inhibitors (acalabrutinib, ibrutinib, zanubrutinib): Consider PJP and acyclovir prophylaxis

JCO. 2020;38:3698-3715
NCCN Guidelines Version 2.2020 Prevention and treatment of cancer-related infections

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