Acute and Chronic Leukemias in the Era of Targeted Therapies

A Review for the Non-Hematologist

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Disclosures

- Advisory Board – AbbVie
- Advisory Board – JADPRO with TG Therapeutics

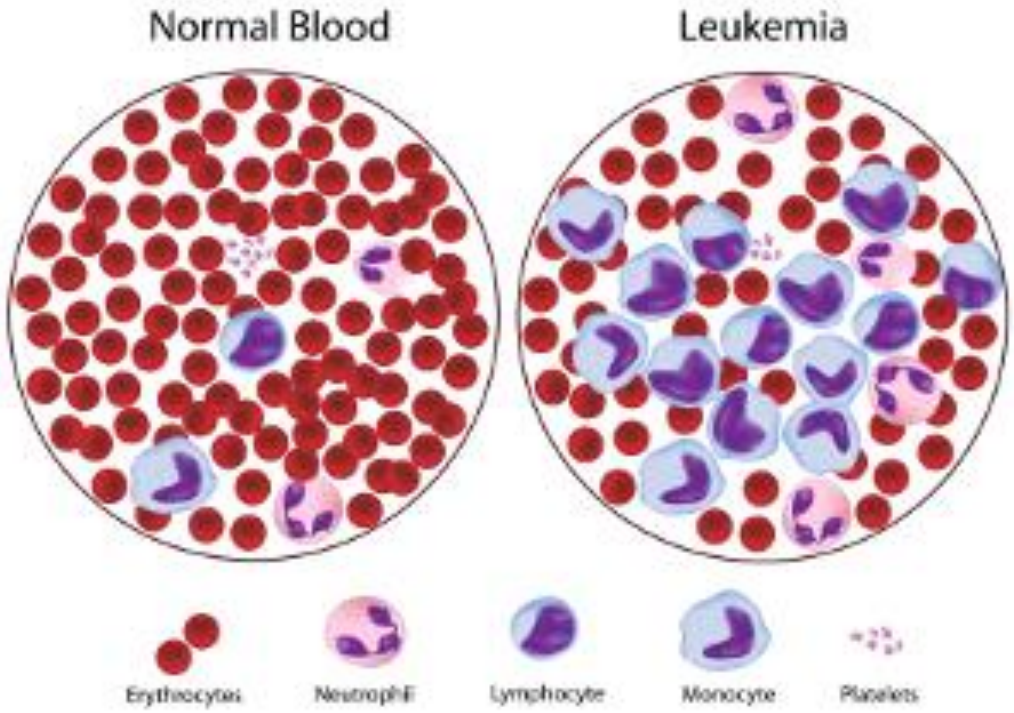
Learning Objectives

1. Describe the basic pathophysiology of Leukemia
2. Compare and contrast common presentations of acute vs. chronic leukemias
3. List drug-drug interactions and side effects of novel targeted therapies in leukemia that are relevant to your practice

Outline

I. Brief Pathophysiology of Leukemia Review
II. Presenting Symptoms of Leukemia
    a. Acute vs. Chronic
III. Novel Oral Targeted Therapies: *review of drug-drug interactions and unique side effects*
    a. TKIs in CML (*dasatinib, imatinib, nilotinib, bosutinib, ponatinib*)
    b. BTK inhibitors in CLL (*ibrutinib, acalabrutinib*)
    c. BCL2 inhibitors in AML and CLL (*venetoclax*)

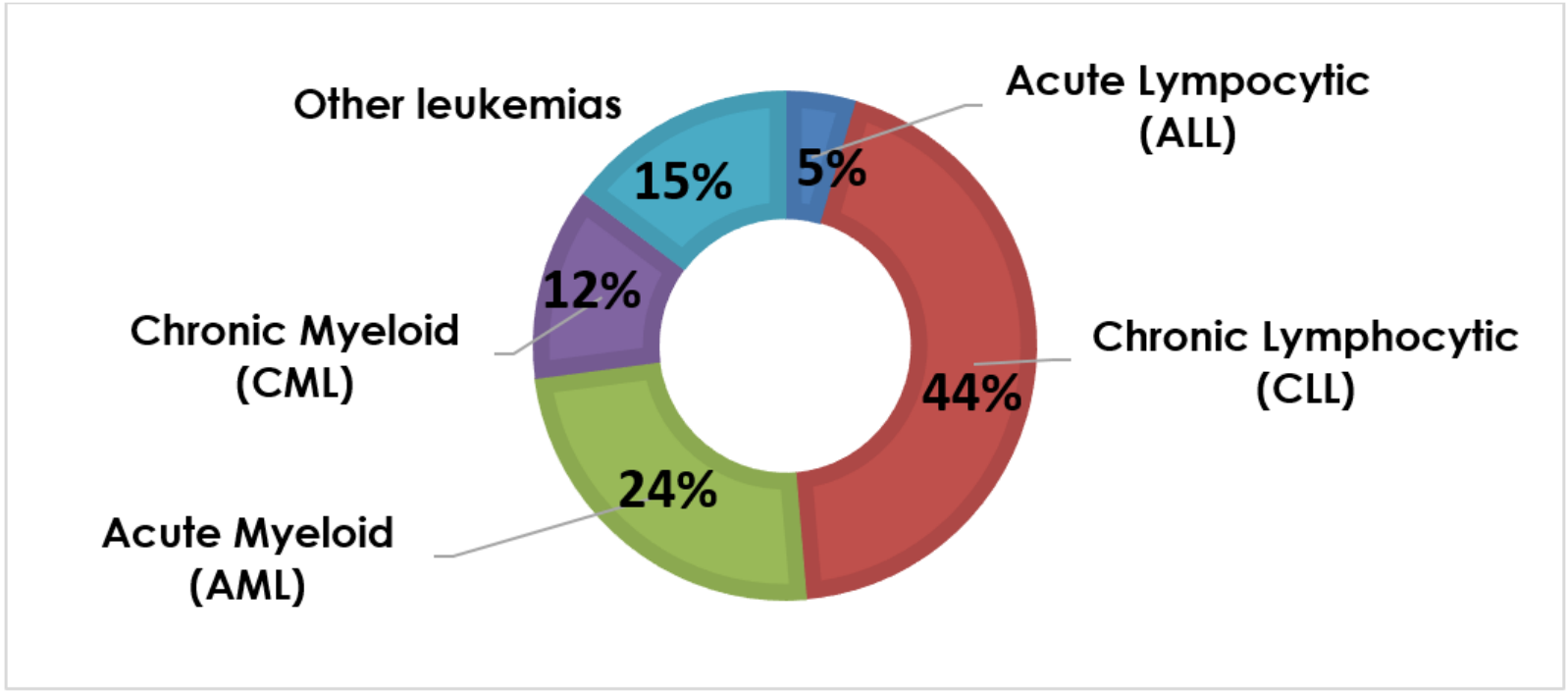
Leukemia = “White Blood”



http://www.physicianassistantexamreview.com/leukemia-lymphoma-multiple-myeloma/

Types of Leukemia

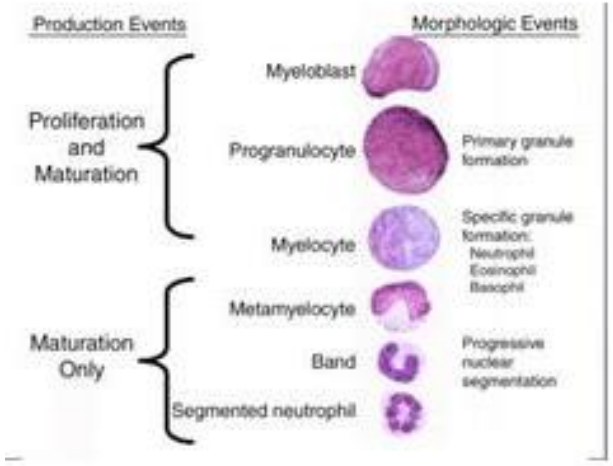
	Myeloid	Lymphoid
Acute	Acute Myeloid Leukemia	Acute Lymphoblastic Leukemia
Chronic	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia



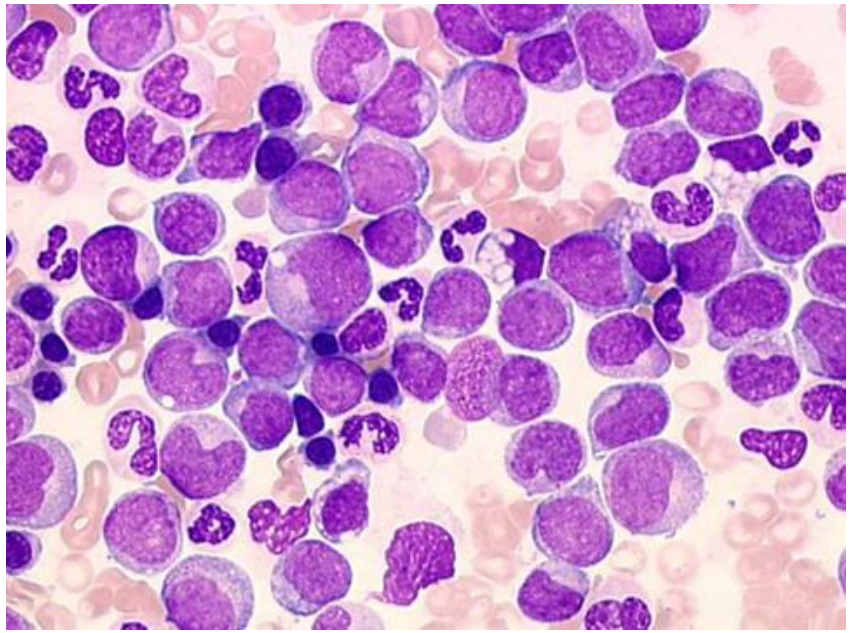
*excluding Quebec ages 15-99 years

http://www.llscanada.org/disease-information/facts-and-statistics#Leukemia

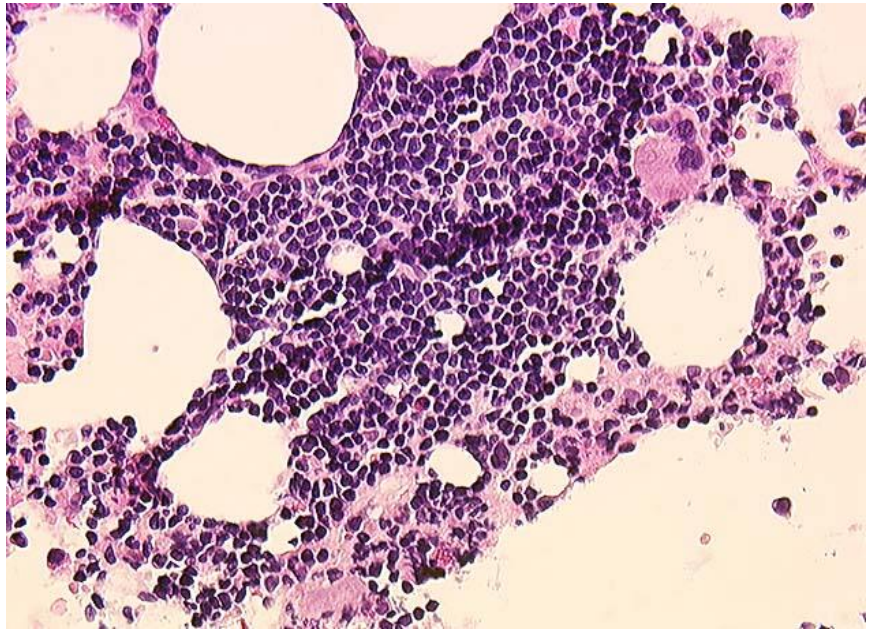
Size Matters in Leukemia!



https://clinicalgate.com/neutrophil-maturation/



http://atlasgeneticsoncology.org/Reports/0219QuilichiniID100006.html



https://path.upmc.edu/cases/case141/images/micro3.jpg

Learning Objectives

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2. Compare and contrast common presentations of acute vs. chronic leukemias
3. List drug-drug interactions and side effects of novel targeted therapies in leukemia that are relevant to your practice

Q: How do patients with leukemia present?

A: It depends!

Acute Leukemia	Chronic Leukemia
Pancytopenia +/- leukocytosis	Often incidental finding of leukocytosis
Symptoms of anemia and thrombocytopenia often present (SOB, bruising, bleeding)	Symptoms of anemia and thrombocytopenia only if late stage disease
Infection	Infection
DIC	AIHA and/or ITP
TLS	Splenomegaly
Blast Crisis	B symptoms

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Go-to Resource

- NCCN Guidelines
  - Free to sign up!

https://www.nccn.org/

Pathophysiology of CML

- Philadelphia chromosome present in 95%
  - t(9;22)
  - Codes for **abnormal tyrosine kinase** that is always “on” resulting in unregulated cell division and leukemogenesis

Tyrosine Kinase Inhibitors (TKIs) in CML

- 3 most commonly used
  - Dasatinib (Sprycel)
  - Imatinib (Gleevec)
  - Nilotinib (Tasigna)

- Less commonly used
  - Bosutinib (Bosulif)
  - Ponatinib (Iclusig)

Let's Get Practical...

Which of the following medications do you use in your daily practice?

- Proton Pump Inhibitors (PPIs)
- H2 antagonists
- Antacids
- Antidepressants (buproprion, citalopram, fluoxetine)
- Amiodarone
- Diltiazem or Verapamil
- Azole antifungals (fluconazole, itraconazole, voriconazole, posaconazole, isuvaconazole)
- Flouroquinolones (levofloxacin, moxifloxacin, ciprofloxacin)
- Gingko balboa, turmeric (curcumin), green tea extract
- St. John's Wort

Common Drug-Drug Interactions with TKIs in CML and Effects on TKI Exposure

Medication	Effect on Dasatinib	Effect on Imatinib	Effect on Nilotinib
Proton Pump Inhibitors (PPIs) Omeprazole Esomeprazole Pantoprazole Lansoprazole	Decrease in exposure	none	Decrease in exposure
H2 antagonists Famotidine Ranitidine	Decrease in exposure, AVOID or space out ≥ 2 hrs after taking TKI	none	Decrease in exposure, AVOID or space out ≥ 2 hrs after taking TKI
Antacids	Decrease if concomitant; take ≥ 2 hrs apart from TKI	none	Decrease if concomitant; take ≥ 2 hrs apart from TKI

Adapted from NCCN guidelines:
https://www.nccn.org/professionals/physician_gls/pdf/cml_blocks.pdf

Common Drug-Drug Interactions with TKIs in CML and Effects on TKI Exposure

Medication	Effect on Dasatinib	Effect on Imatinib	Effect on Nilotinib
Antidepressants buproprion citalopram fluoxetine	Minor increase, consider QTc monitoring	Minor increase, consider QTc monitoring	AVOID d/t cumulative QTc prolongation risk
CV medications amiodarone diltiazem verapamil	Increase in exposure and arrhythmia risk, consider alternative CV med or TKI dose adjustment	Increase in exposure, consider alternative CV med or TKI dose adjustment	AVOID d/t cumulative QTc prolongation risk

Adapted from NCCN guidelines:
https://www.nccn.org/professionals/physician_gls/pdf/cml_blocks.pdf

Common Drug-Drug Interactions with TKIs in CML and Effects on TKI Exposure

Medication	Effect on Dasatinib	Effect on Imatinib	Effect on Nilotinib
Azole antifungals Fluconazole (≥ 200mg) Posaconazole Voriconazole Itraconazole Isuavaconazole	Increase in exposure, strongly consider alternative agent or TKI dose adjustment	Increase in exposure, strongly consider alternative agent or TKI dose adjustment	Increase in exposure, strongly consider alternative agent or TKI dose adjustment
Flouroquinolones Levofloxacin Moxifloxacin Ciprofloxacin	QTc monitoring	none	Use with caution

Adapted from NCCN guidelines:
https://www.nccn.org/professionals/physician_gls/pdf/cml_blocks.pdf

Common Drug-Drug Interactions with TKIs in CML and Effects on TKI Exposure

Medication	Effect on Dasatinib	Effect on Imatinib	Effect on Nilotinib
Herbal supplements Gingko Balboa, Turmeric (curcumin), Green Tea Extract	Increase in exposure, strongly consider supplement discontinuation	Increase in exposure, strongly consider supplement discontinuation	Increase in exposure, strongly consider supplement discontinuation
St. John's Wort	Decrease in exposure, AVOID	Decrease in exposure, AVOID	Decrease in exposure, AVOID

Adapted from NCCN guidelines:
https://www.nccn.org/professionals/physician_gls/pdf/cml_blocks.pdf

What Matters to You

Which medication(s) that you commonly use in your daily practice can interact with TKI treatments for your patients with CML?

Class Effects of TKIs in CML

- Lower extremity edema
- Diarrhea
- Elevated LFTs
- QT prolongation
- Rash

Toxicity	Imatinib	Nilotinib	Dasatinib
Edema	++	-	++
GI toxicity	++	+	+
Headache	+	++	+
Musculoskeletal pain/ Cramps	++	+	+
Pericardial Effusions	+	-	++
Pleural Effusions	+	-	++
Pulmonary Arterial Hypertension	-	-	+
QT Prolongation	-	++	+
Rash	++	++	+
Liver abnormalities	++	++	+
Elev Lipase/Glucose	-	++	-

A Brief Word on Less Commonly Used TKIs in CML

- Bosutinib (Bosulif) is used less commonly due to high propensity for diarrhea and hepatotoxicity
  - Increased awareness of this medication in your patients who drink or use large amounts of Tylenol
- Ponatinib carries a high risk of vascular complications
  - optimizing BP control, weight, diabetes control, can help decrease this risk

Patient #1

- A 64 year old male with hypertension and CML calls in regarding new lower extremity edema. His medications include amlodipine (Norvasc) and imatinib (Gleevec). What are some considerations on your differential?

Patient #2

- A patient with a history of atrial fibrillation, hypertension, depression, and CML presents for follow-up after obtaining an EKG for palpitations. EKG reveals normal sinus rhythm with occasional premature atrial contractions, and prolonged QT. Her up to date medication list is below. Which of her medications may be contributing to the prolonged QTc?

Metoprolol succinate
Lisinopril
Fluoxetine
Nilotinib

Take-Home Points for CML Patients on TKIs

- Reach out to your patient's hematologist/oncologist - we're here to help!
  - Peri-procedural recommendations
  - Questions of compliance
- NCCN guidelines are another great resource
- When starting a patient with CML on a new medication, ensure to **check for drug-drug interactions**
- **Most common side effects:**
  - **Lower extremity edema**
  - **GI side effects**
  - **Elevated LFTs**

Switching Gears...

CLL: Partnership with the PCP

- Increased risk of secondary malignancies in CLL, including a **6-8x higher risk of nonmelanoma skin cancer**
  - Ensure patients stay up to date on regular age-appropriate cancer screening
    - Colorectal cancer screening, mammogram, PSA
  - Regular full body skin exams
- CLL patients are immunosuppressed regardless of treatment status
  - Importance of all regularly recommended vaccinations
  - **No live vaccines!**

Novel Oral Agents in CLL

- Bruton's Tyrosine Kinase (BTK) Inhibitors
  - Ibrutinib (Imbruvica)
  - Acalabrutinib (Calquence)
- BCL2 Inhibitors
  - Venetoclax (Venclexta)
- PI3K Inhibitors
  - Idelalisib (Zydelig)
  - Duvelisib (Copiktra)

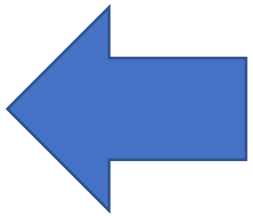
Back to You…

- Which of the following medications do you see or use most commonly in your practice?
  - Azole antifungals (fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole)
  - Clarithromycin
  - Carbamazepine
  - Rifampin
  - St. John's Wort
  - Phenytoin
  - Diltiazem or Verapamil

Drug Drug Interactions with BTK inhibitors in CLL

- Metabolized via CYP3A
  - **Check for interactions before starting a new medication**
  - If moderate CYP3A inhibitors are needed, discuss with the patient's hematologist/oncologist - we may need to reduce the ibrutinib dose
  - Strong CYP3A inhibitors should be avoided – consider alternative agent

Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
Fluconazole	St. John's Wort
Clarithromycin	Carbamazepine
Diltiazem	Rifampin
Verapamil	Phenytoin
	Voriconazole, Posaconazole, Itraconazole



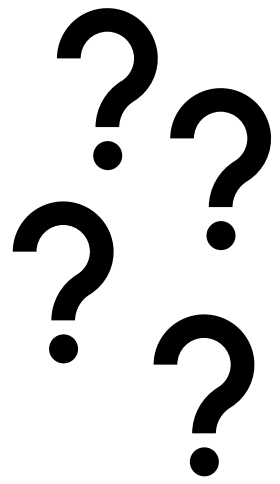
Which of these apply to your practice?

Class Effects of BTK inhibitors in CLL*

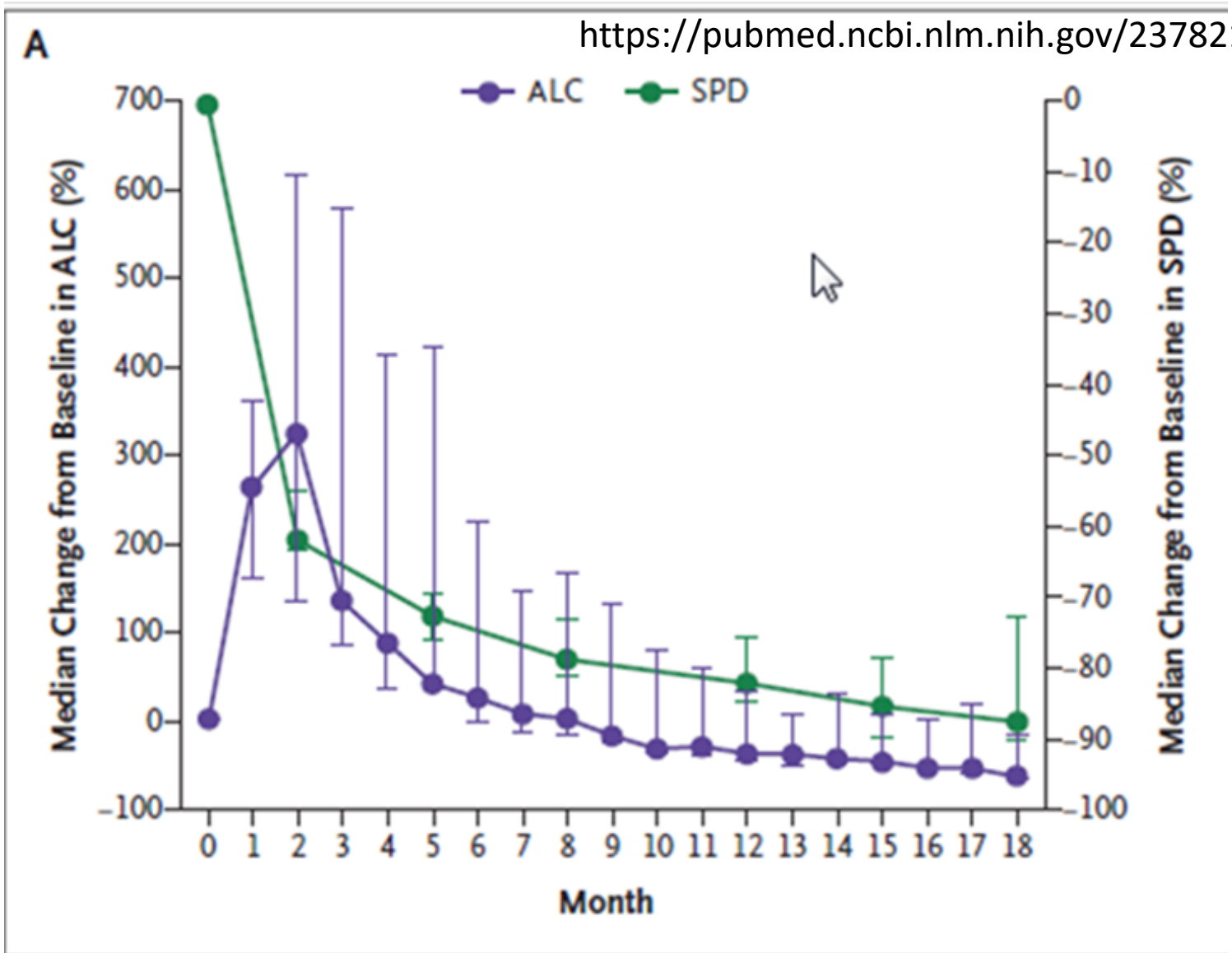
- Bruising and bleeding
  - Reversibly impairs platelet function (but PT/INR/aPTT are usually normal)
  - **Hold for 3-7 days pre and post-procedures**
- Hypertension
  - Especially over time; be aware of drug-drug interactions with diltiazem and verapamil
- Atrial Fibrillation
  - **Avoid warfarin**, DOACs preferred w/ibrutinib dose reduction
  - Rare ventricular arrhythmias have also been observed
- Fungal Infections
  - No current role for antifungal prophylaxis

*Less common with acalabrutinib than ibrutinib

BTKi-related Redistribution Lymphocytosis



https://pubmed.ncbi.nlm.nih.gov/23782158/



Patient #3

- 68M with CLL on ibrutinib presents with a week long history of fever (Tmax 39.3C), dry cough, and malaise. He is not neutropenic and CXR is unremarkable. Ultimately, a chest CT is ordered for further evaluation:

Patient #3 Continued…

- Infectious Diseases was consulted and recommended a bronchoscopy for further evaluation. How soon can he undergo this procedure on a non-emergent basis?
  a. ASAP
  b. Tomorrow
  c. 3 days
  d. 7 days

IDSA Call to Action: Fungal Infections on Ibrutinib

- Since ibrutinib's approval, multiple case reports have emerged citing early development of invasive fungal infections (IFI)
  - **Median time to diagnosis** of IFI: **3 months**
- Most frequent IFI = **pulmonary aspergillosis**
  - Cryptococcus, PJP, histoplasma, mucormycosis, fusarium have also been reported
- Recall that CLL itself is an immunodeficient state, and many of the patients who received ibrutinib when it first came out were heavily pretreated
  - ibrutinib is now commonly used in frontline therapy; can happen with frontline therapy as well

Patient #4

- A 64 year old female with hypertension, obesity, type 2 diabetes, and CLL presents with newly diagnosed atrial fibrillation. Her medications are listed below. What is the most appropriate anticoagulation strategy in this patient?

<u>Med List</u>
lisinopril
ibrutinib
acyclovir
metoprolol

a. Warfarin
b. Aspirin
c. DOAC
d. None – anticoagulation is contraindicated in CLL patients on ibrutinib

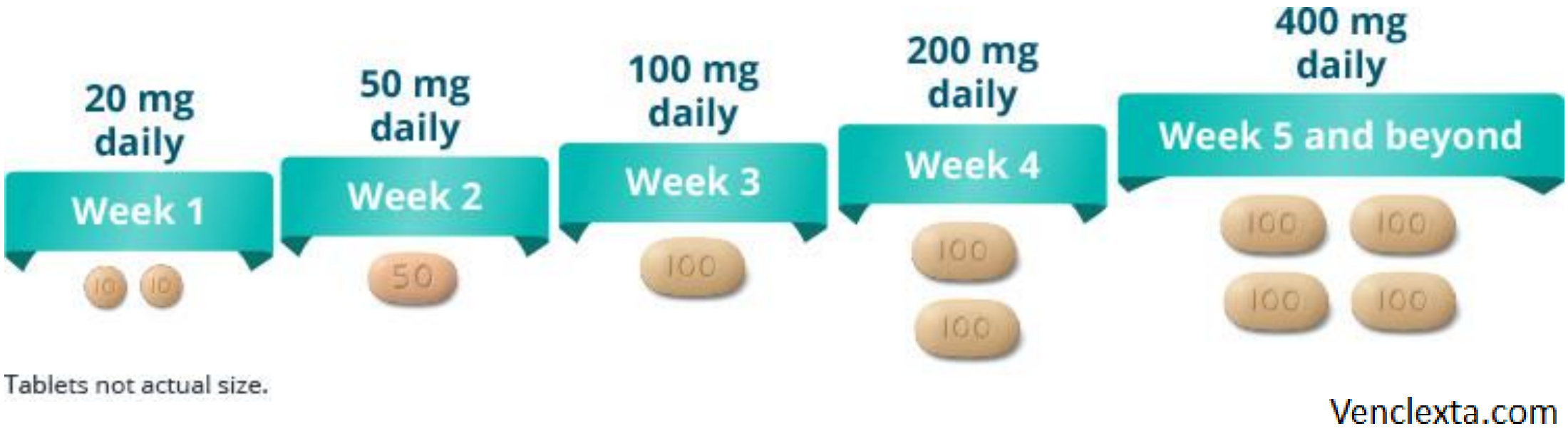
Take-Home Points for BTK inhibitors in CLL

- The hematologist is your friend – we're here to help!
- **Drug-Drug Interactions** via CYP3A
- **Need to be held for 3-7 days pre- and post-procedurally** to minimize risk of bleeding
- Can be associated with atrial fibrillation
  - AVOID warfarin; DOACs preferred
- White count often initially goes up after starting therapy
  - "Redistribution Lymphocytosis"
- Keep fungal infections on your differential

BCL2 Inhibitors in AML and CLL

- Venetoclax (Venclexta)
- BCL2 protein impairs apoptosis, allowing unchecked cell division
  - i.e. the brakes are broken
  - Inhibiting BCL2 "fixes the brakes", restoring apoptosis

Tumor Lysis Syndrome and Dose Escalation Protocols



- This is of particular concern in patients with CLL, although newer regimens are being administered in ways that mitigate the risk to some degree

What Matters to You

Which of the following medications do you use often in your practice?

CYP3A4 Inhibitors	CYP2D6 Inhibitors	p-glycoprotein inhibitors
clarithromycin erythromycin diltiazem verapamil itraconazole ketoconazole	buproprion fluoxetine paroxetine terbinafine	cyclosporine tacrolimus ketoconazole verapamil quinidine

Drug-Drug Interactions with BCL2 inhibitors in AML and CLL

- Caution or contraindicated with CYP3A4, CYP2D6, and p-glycoprotein inhibitors
  - Work with pharmacy and your patient's hematologist

Which medication(s) that you use often in your practice can interact with the BCL2 inhibitor venetoclax (Venclexta) in patients with AML or CLL?

Class Effects of BCL2 inhibitors in AML and CLL

- Tumor Lysis Syndrome at initiation
  - Increased risk in patients with impaired renal function
- GI side effects
- Cytopenias
  - Neutropenia

Patient #5

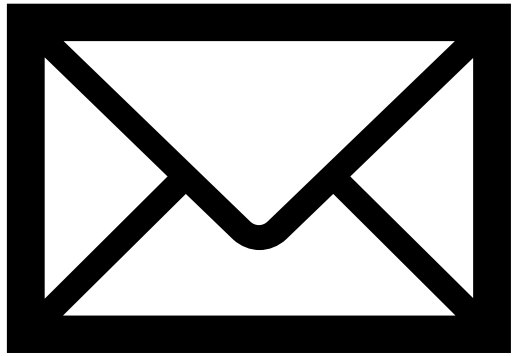
- A 72 year old male with CLL was recently hospitalized for initiation of venetoclax dose escalation protocol to monitor for TLS. He calls in with complaint of new onset diarrhea and nausea. What is on your differential?

Take Home Messages for Oral Therapies in Acute and Chronic Leukemias

- Evaluate for **drug-drug interactions** before starting a new medication
- Partner with the patient's hematologist
  - Potential side effects
  - Peri-procedural recommendations – does the drug need to be held?
- NCCN Guidelines are free to sign up for and a great resource

Questions?

- Email hesse.amber@mayo.edu



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- To you!!
- AAPA
- Dr. Call
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