Trillium Health Partners
Better Together

Managing Select Complications in Oncology

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Presenter Disclosure

- Presenter's Name: Sonia Cheung
- I have no real or potential conflict to disclose.
- Speaking Fees for current program:
  - I have received no speaker's fee for this learning activity

Goal

- The goal of this session is to provide a concise review of select complications in oncology and provide the audience with clinical pearls that they can take back to their hospital practice.

Objectives

By the end of this session, you should be able to:

- Discuss the initial management of these commonly encountered complications in oncology:
  - Hypercalcemia of malignancy
  - Tumor lysis syndrome
  - Cancer-associated thrombosis

Hypercalcemia of Malignancy

Ca^{2+}

Ca^{2+}

Ca^{2+}

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Hypercalcemia of malignancy – Who?

- Incidence
  - Experienced by 20-30% of all cancer patients
  - Cancer patients with hypercalcemia > ⅓ of cases of hypercalcemia that present to ER
  - Cancer types: breast, lung, bone, multiple myeloma, lymphoma, kidney

Thomas 2016

Mechanisms of hypercalcemia – How?

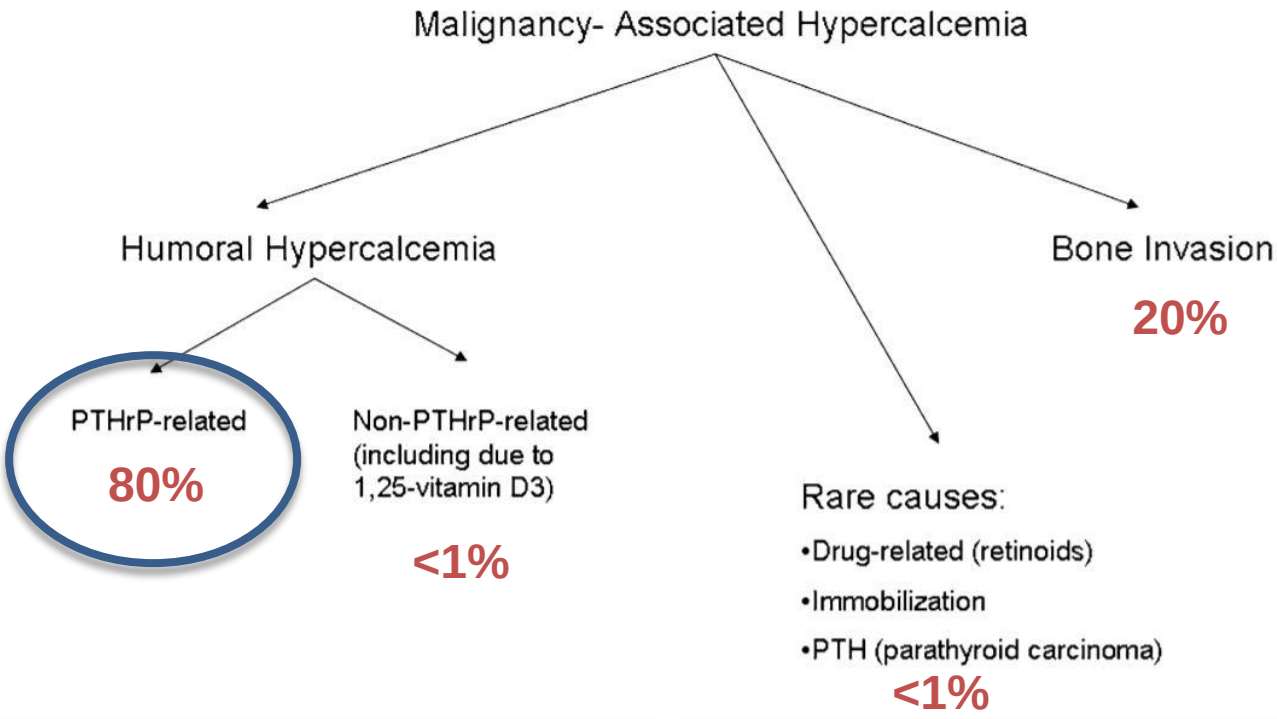
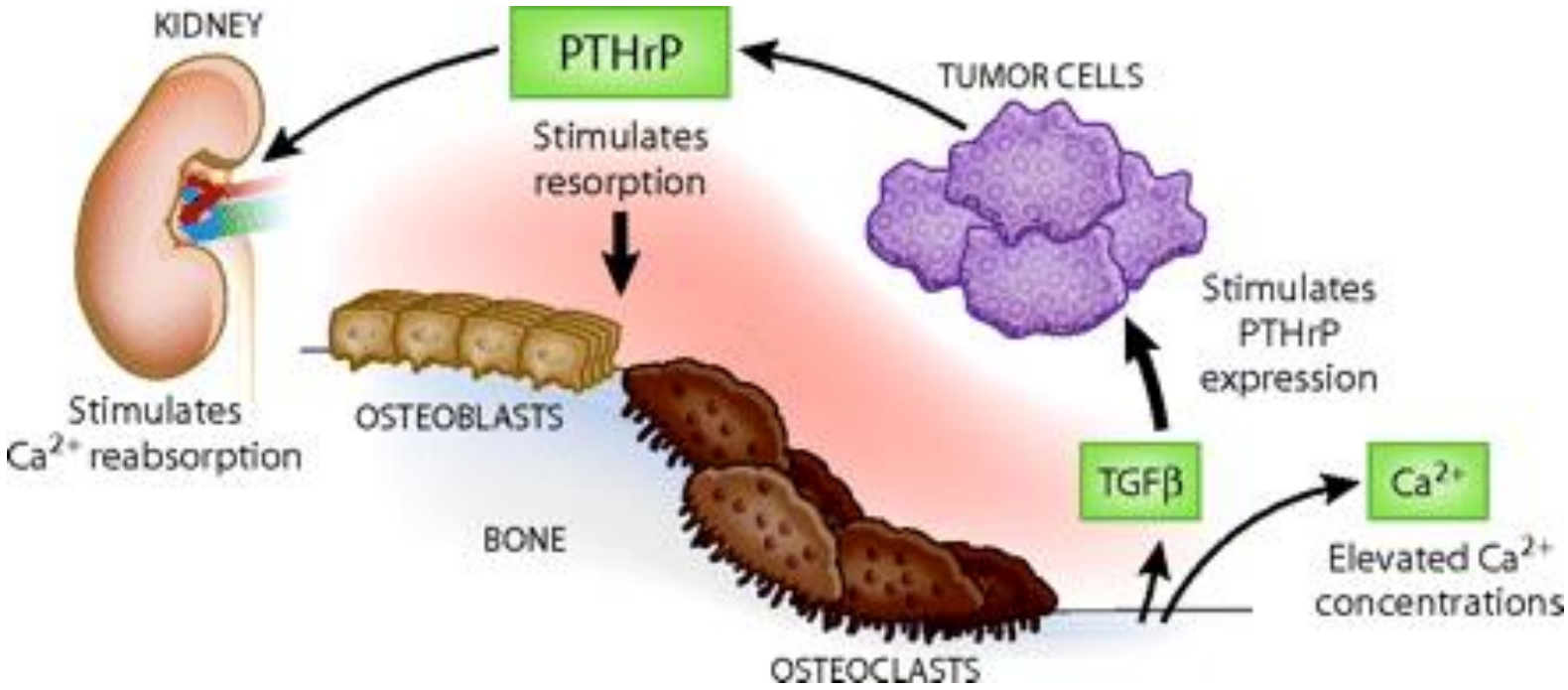


Figure 1. | **Mechanism of malignancy-associated hypercalcemia.** PTHrP, parathyroid hormone–related hormone.

Rosner 2012

Systemic secretion of PTHrP



http://jasn.asnjournals.org/content/19/4/672/F1.expansion

Hypercalcemia - Diagnosis

- Total serum calcium level (and current serum albumin)
- Serum ionized calcium level
- Rule out other causes of elevated calcium unrelated to cancer (primary hyperparathyroidism, use of thiazide diuretics, granulomatous disease)
- Serum phosphorus
- Parathyroid hormone (PTH)
- Parathyroid hormone-related peptide (PTHrP)
- 1,25-dihydroxy vitamin D ($1,25[OH]_2D$)
- 25(OH)D
- Bone scan (or skeletal survey in multiple myeloma)

Goldner 2016

Hypercalcemia - Clinical presentation

Table 1. Symptoms of moderate to severe hypercalcemia associated with cancer and anticancer treatments.

	Early Manifestations	Later Manifestations
Neurological	• weakness/fatigue • memory/concentration difficulty	• drowsiness/confusion • delirium → coma
Cardiovascular	• shortened QT_c interval • enhancement of digitalis effects	• ST segment elevation • hypotension • bradyarrhythmias → heart block → cardiac arrest
Gastrointestinal	• anorexia • constipation	• nausea • vomiting
Genitourinary	• polyuria and nocturia	• dehydration → oliguria

Very poor prognosis!
50% of patients die within 30 days

Median duration of survival
2-6 months
from onset of hypercalcemia

Alberta Health Services 2014
Goldner 2016
Rosner 2012

Hypercalcemia – Principles of Management

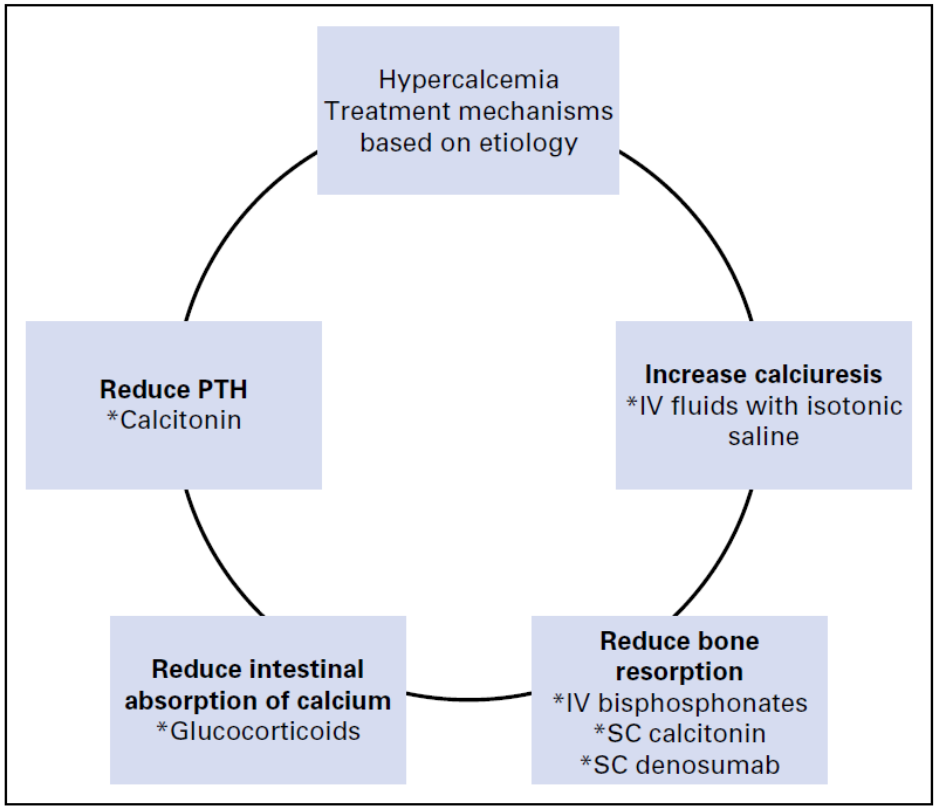


FIG 1. A treatment approach for hypercalcemia of malignancy. *Treatment mechanism. IV, intravenous; PTH, parathyroid hormone; SC, subcutaneous.

Goldner 2016

Hypercalcemia - Management

- Depends on severity and rate of ascent of the serum calcium level
- General classification:
  - Mild 2.6-2.9 mmol/L
  - Moderate 3.0-3.4 mmol/L
  - Severe 3.5 mmol/L or greater
- Rapid increase in serum calcium: marked neurologic dysfunction
- Chronic slow increase: minimal neurologic symptoms
- Anti-hypercalcemia therapy alone does not have any effect on mortality

Hypercalcemia - Management

- General supportive measures
  - Removal of calcium from parenteral feeding solutions
  - Discontinuation of all calcium and vitamin D supplements
  - Discontinuation of sedative medications → enhance mental clarity
  - Hypophosphatemia common, replace phosphorus PO or NG if possible → target 0.98-1.0 mmol/L

Thomas 2016

Hypercalcemia – Management

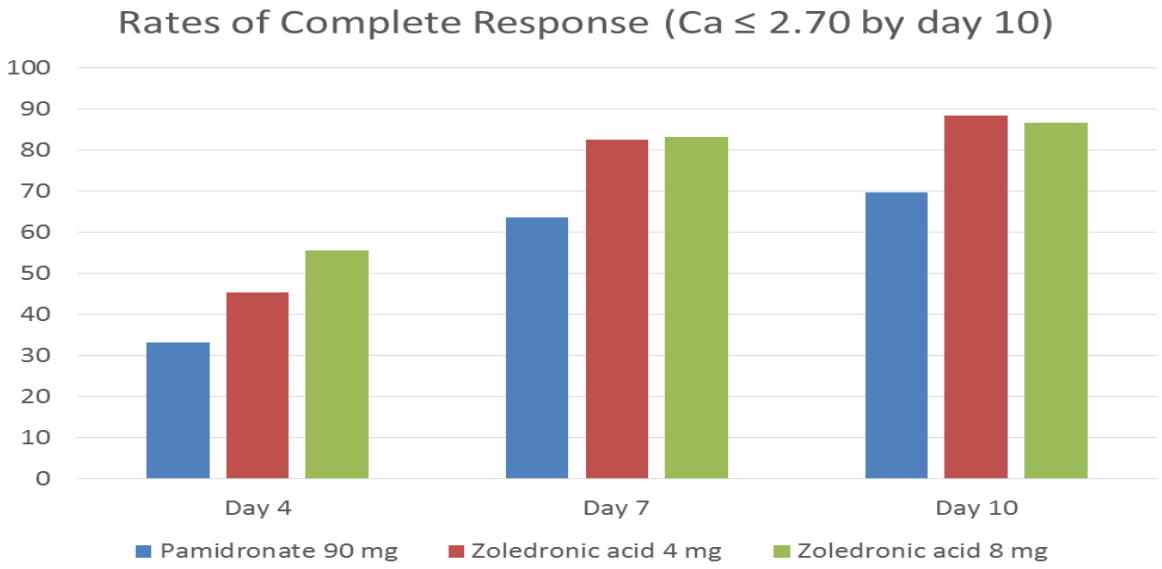
- Saline hydration and calciuresis: 200-500 ml/hr, adjust to urine output 100-150 ml/hr
  - Consider baseline dehydration and renal function, cardiovascular status, degree of neurologic impairment, severity of hypercalcemia
- Intravenous Bisphosphonates → 1st line, mainstay for long-term
  - Pamidronate (2-4 hrs, $10), Zoledronic acid (15 mins, $25)
  - Block osteoclastic bone resorption
  - Initiate as soon as hypercalcemia is diagnosed, response takes 2-4 days
  - 60-90% of patients have normalized serum calcium within a week
  - Duration of response: 1-3 weeks
  - Potential side effects: hypophosphatemia, hypomagnesemia, hypocalcemia, influenza-like symptoms, nephrotoxicity, osteonecrosis of the jaw

Ralston 1990
Goldner 2016

Hypercalcemia – Pamidronate vs. Zoledronic acid

Major P, Lortholary A, et al. J Clin Oncol 2001; 19:558-67.

- Patients with corrected serum calcium 3.00 mmol/L or greater were treated with single dose of zoledronic acid 4 mg, 8 mg, or pamidronate 90 mg
- Rate of complete response by day 10, response duration, and time to relapse were measured.
- 287 patients randomized and evaluated for safety, 275 evaluated for efficacy



Hypercalcemia - Management

- Glucocorticoids
  - Inhibit osteoclastic bone resorption by decreasing tumor productive of locally active cytokines
  - May have a role in lymphoma where there may be excessive vitamin D or endogenous overproduction of calcitriol
  - Prednisone 60 mg daily x 10 days or IV Hydrocortisone 200 mg x 3 days
  - Not commonly used

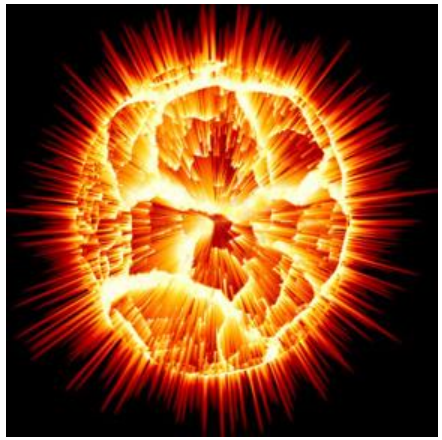
- Calcitonin
  - Increases renal excretion of calcium, inhibits decreasing bone resorption by interfering with osteoclast function
  - Negligible toxicity
  - Rapid onset of action
  - Short duration of action, tachyphylaxis in ~48 hrs due to downregulation of calcitonin receptors

Thomas 2016

Hypercalcemia - Management

- Denosumab
  - Human monoclonal antibody to RANKL
  - Reduces osteoclast activity and bone resorption
  - Use in hypercalcemia of malignancy is reserved for cases refractory to zoledronic acid or in patients with severe renal impairment
  - Ideal dose in renal impairment is unknown → one case series in patients with multiple myeloma and renal impairment resulted in one patient having persistent hypocalcemia after denosumab treatment, requiring IV calcium supplementation
  - Start with conservative dosing at 0.3 mg/kg
- Cinacalcet
  - Calcimimetic that activates the calcium-sensing receptor
  - Only 2 case reports on successful use of cinacalcet in this population (pts were refractory to all other treatment options)
- Dialysis
  - last resort

Tumor Lysis Syndrome



Tumor lysis syndrome – What and Who?

- Results in massive cellular breakdown in rapidly proliferating, bulky or highly chemo-sensitive tumors, and release of intracellular contents into the bloodstream resulting in metabolic abnormalities
- 3 categories of factors to consider in assessing risk

Tumor-related	Patient-related	Treatment-related
Burkitt's lymphoma Non-Hodgkin's lymphoma	Elevated uric acid	Cytarabine, etoposide, cisplatin
Acute myeloid leukemia Acute lymphocytic leukemia	Renal dysfunction	Corticosteroids
Chemosensitive tumors (eg. Small cell lung) High tumor burden	Tumor infiltration into kidney	Radiation
Highly proliferative tumors	Advanced age	Monoclonal Ab
Elevated LDH	Obstructive uropathy	

Coiffier 2008

TLS – Definition

Table 1. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change From Baseline
Uric acid	≥ 476 μmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25%decrease

NOTE. Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy.

Clinical TLS is present when laboratory TLS is accompanied by one or more of cardiac arrhythmia, death, seizure, or AKI with elevated Scr > 1.5 times the ULN

Coiffier 2008
Edeani 2016

TLS - Pathophysiology

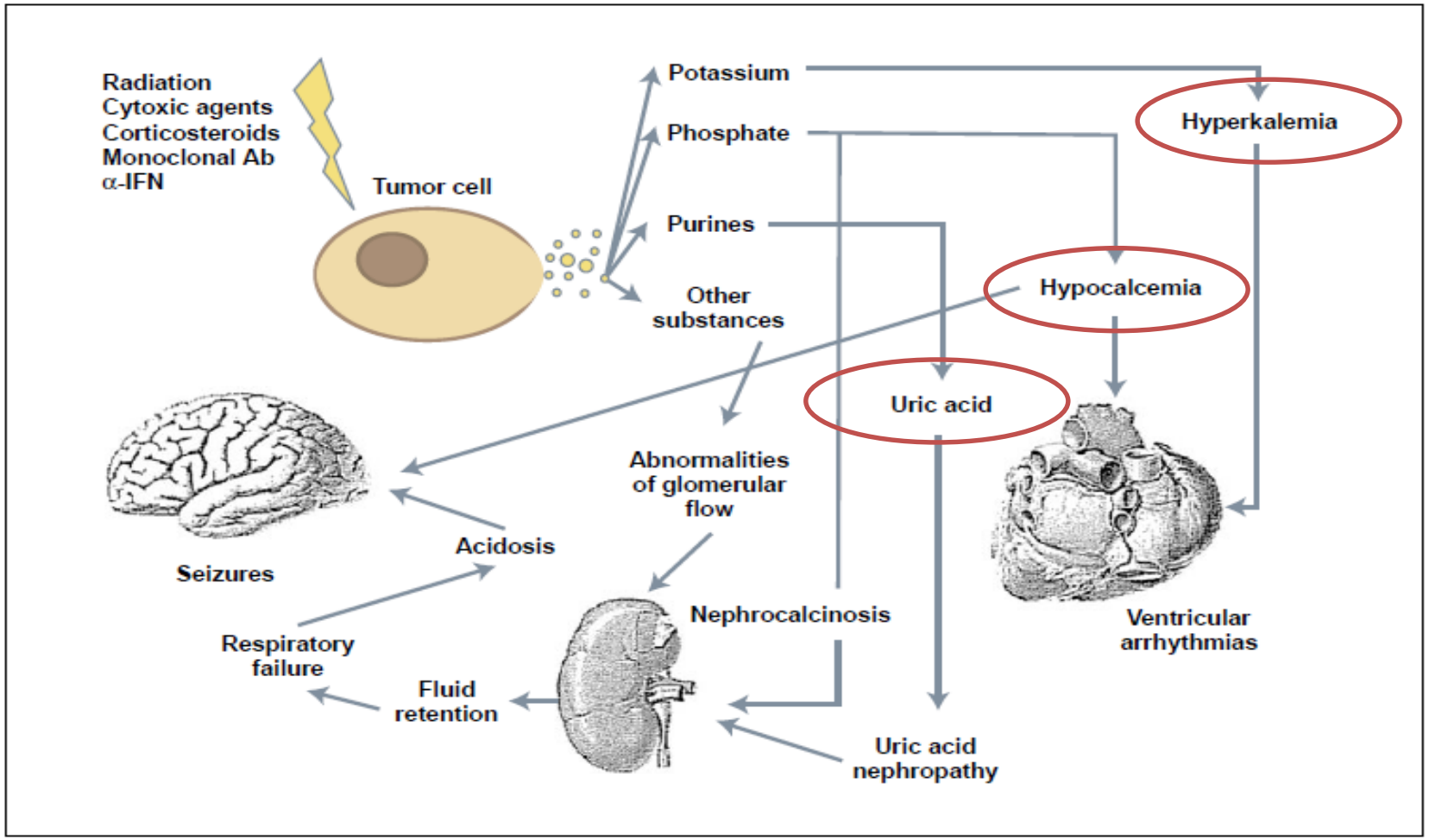


Figure 1. The pathophysiology of tumor lysis syndrome.[1]

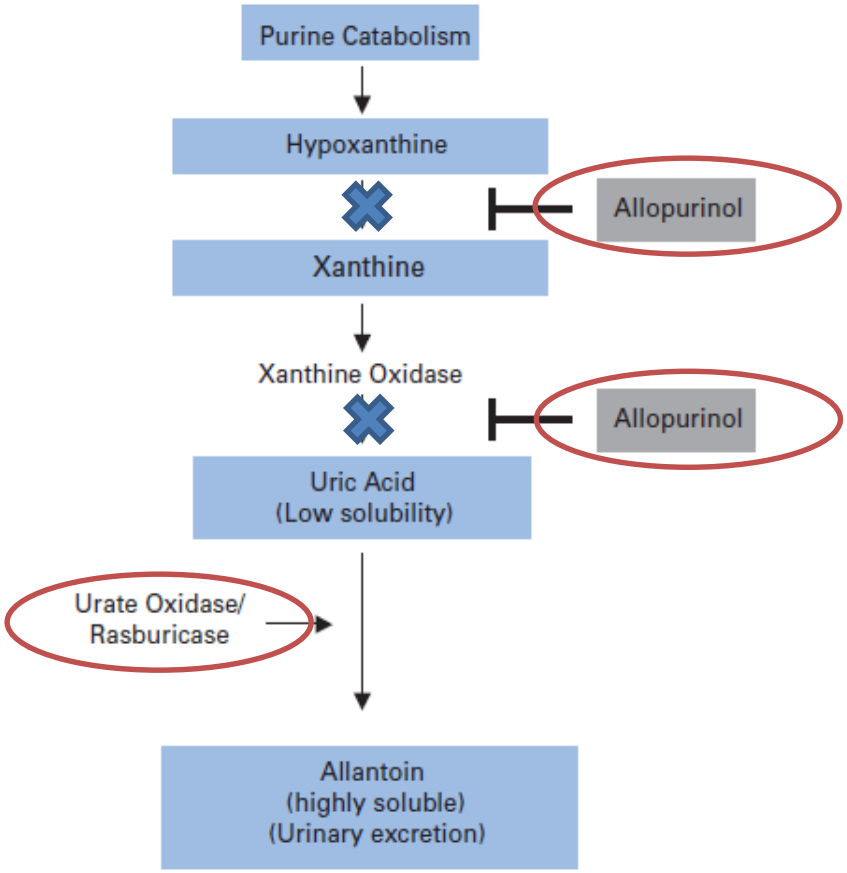
Ab=antibody; α-IFN=interferon α.

Cheson 2009

TLS – Clinical Manifestations

- Central nervous system
  - Seizures, syncope, lethargy, mental status changes
- Cardiovascular
  - Edema, fluid overload, congestive heart failure, arrhythmias, sudden death, hypotension, cardiac arrest
- Gastrointestinal
  - Nausea, vomiting, diarrhea, anorexia
- Neuromuscular
  - Muscle cramps, tetany, paresthesias
- Renal
  - Hematuria, oliguria, anuria, acute renal failure

TLS - Hyperuricemia



Coiffier 2008

TLS – Hyperuricemia

Allopurinol

- Blocks xanthine oxidase, which converts hypoxanthine to xanthine, and xanthine to uric acid
- Usual dose: 300 mg po daily, dosage adjustment required for renal insufficiency
- Allopurinol prevents formation of new uric acid, it does not reverse uric acid that has already been made, this may result in delay of effect.
- Cost per day: $0.21

Rasburicase

- Recombinant urate oxidase, an enzyme which oxidizes uric acid to allantoin which can be easily excreted in urine
- Demonstrates a complete elimination of uric acid, thus no delay in effect
- Usual dose: 0.15 - 0.2 mg/kg IV daily for up to 7 days (numerous protocols exist)
- THP standardized dose: 4.5 mg ~ $410

TLS - Prevention

- PREVENTION IS KEY
- Hydration and diuretics
  - Initiate hydration 12-24 hrs pre-treatment, continue 48-72 hrs post-
  - Target urine output 80-100 mL/m^2/hr
- Allopurinol or Rasburicase
- Sodium bicarbonate no longer recommended
- Supportive treatment

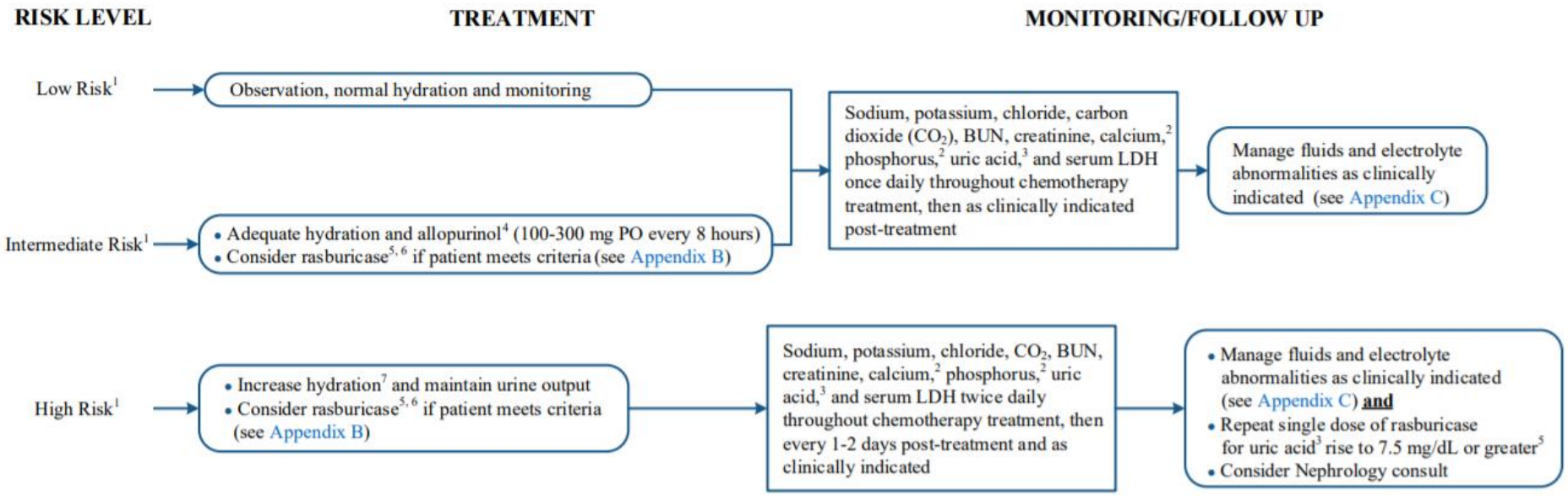
TLS - Treatment

- Supportive measures:
  - Removal of potassium and phosphate sources (IV fluids/feeds/medications)
  - Sodium polystyrene sulfonate
    - Potassium ≥ 6.0 mmol/L and symptomatic
  - Insulin-Glucose therapy, Calcium gluconate, Inhaled beta-agonist, Diuretics
    - Potassium ≥ 7.0 mmol/L and symptomatic
  - Phosphate binders via PO or NG route
  - Calcium gluconate IV
    - Severe symptomatic hypocalcemia
  - Dialysis
    - Severe acute renal failure

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

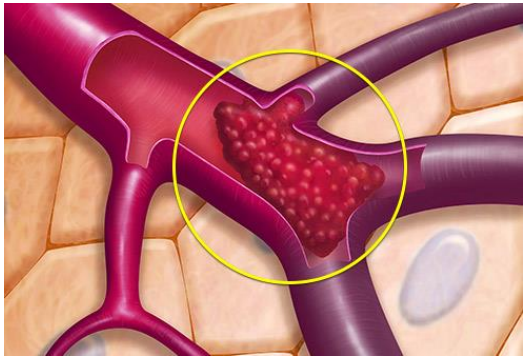
Tumor Lysis Syndrome (TLS) in Adult Patients

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*



https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-tumor-lysis-web-algorithm.pdf

Cancer-Associated Thrombosis (CAT)



https://www.webmd.com/dvt/ss/slideshow-thrombosis-types

Thrombosis and Cancer go hand-in-hand

Cancer patients have a 4- to 7-fold increased risk of VTE

Cancer patients have a 2-fold increased risk of major hemorrhage on anticoagulation

VTE is the 2nd leading cause of death in cancer patients, behind cancer itself

Cancer is associated with 20-30% of VTE in population studies

Wang 2018

Cancer-Associated Thrombosis: Who?

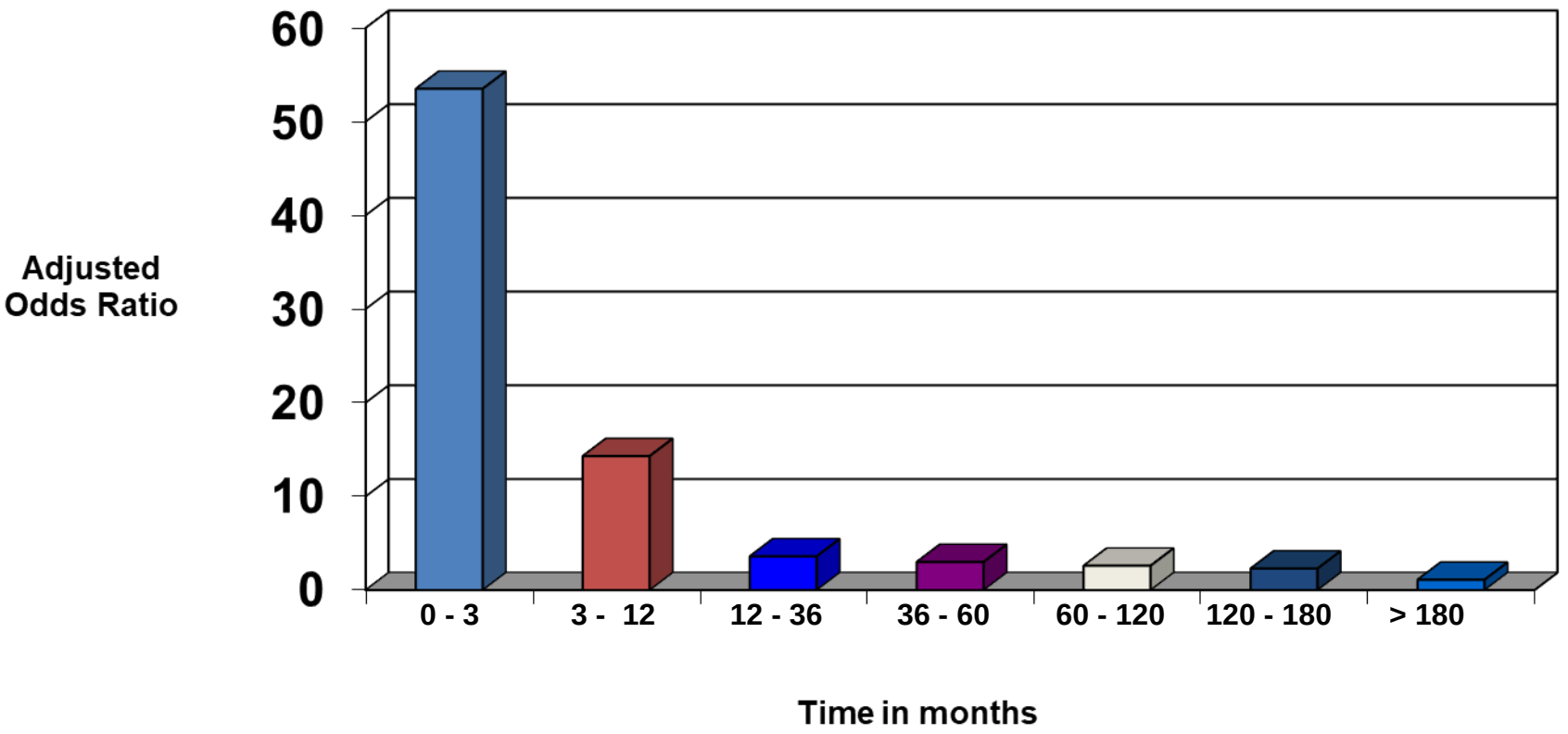
Table 3. Risk Factors and Biomarkers for Cancer-Associated Thrombosis

Cancer Related	Treatment Related	Patient Related	Biomarkers
Primary site	Chemotherapy	Older age	Platelet count (≥ 350,000/μL)
Stage (higher for advanced stage)	Antiangiogenic agents (eg, thalidomide, lenalidomide)	Race (higher in African Americans; lower in Asians/Pacific Islanders)	Leukocyte count (> 11,000/μL)
Cancer histology (higher for adenocarcinoma than squamous cell)	Hormonal therapy	Medical comorbidities (infection, renal disease, pulmonary disease, arterial thromboembolism)	Hemoglobin (< 10 g/dL)
Time after initial diagnosis (highest in first 3 to 6 months)	Erythropoiesis-stimulating agents Transfusions Indwelling venous access devices Radiation therapy Surgery > 60 min	Obesity History of VTE Diminished performance status Inherited prothrombotic mutations	

Abbreviation: VTE, venous thromboembolism.

Lyman 2013

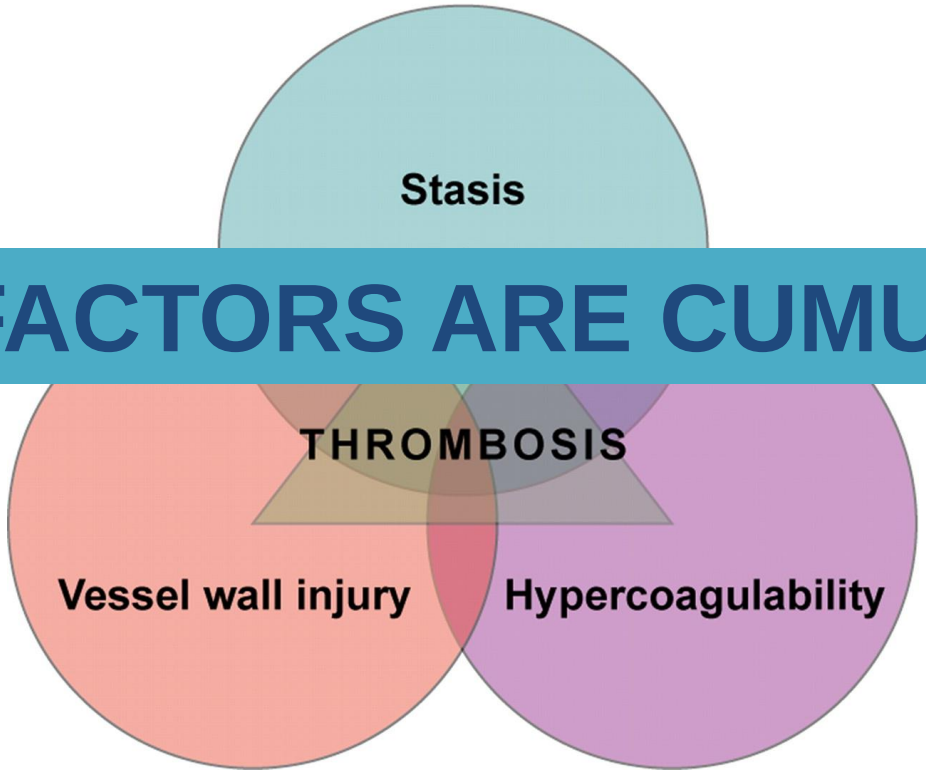
Risk of VTE and Time after Diagnosis of Cancer



Blom 2005

Thrombosis: How?

Virchow's Triad



RISK FACTORS ARE CUMULATIVE!!

Kyrle 2009

Thrombosis - Diagnosis

- Venous ultrasonography
- Computed tomography pulmonary angiography (CTPA)
- Ventilation / Perfusion (V/Q) lung scan
- Venography
- D-dimer
- Magnetic resonance imaging (MRI)

Is it a clot or ….???

Common causes of swollen legs in a palliative patient
Unilateral
• deep vein thrombosis
• cellulitis
• nodal disease in groin
• lymphedema
Bilateral
• deep vein thrombosis
• hypoalbuminemia
• heart failure
• medications (steroids, nifedipine)
• lymphoedema
• pelvic disease causing reduced venous outflow

Common causes of dyspnea in advanced cancer

- Pneumonia
- Pulmonary edema
- Pleural effusion
- anemia
- lung metastases
- lymphangitis
- muscle fatigue
- concurrent pulmonary illness
  - COPD
  - emphysema
  - interstitial lung disease

Noble 2007

CAT – Treatment (LMWH vs VKA)

- CLOT NEJM 2003:
  - dalteparin provides significant reduction in VTE recurrence compared to warfarin (9% vs 17%)
  - no difference in major bleeding

- CATCH JAMA 2015:
  - a nonsignificant reduction in VTE recurrence between tinzaparin and warfarin (6.9% vs 10%)
  - tinzaparin significantly decreased the risk of clinically relevant non-major bleeding (CRNMB)

CAT – Treatment (LMWH vs DOACs)

Hokusai VTE Cancer study 2018

- Open-label, randomized, noninferiority study
- 1046 cancer patients (dx within 2 yrs)

- LMWH x 5 days, followed by Edoxaban 60mg (or 30mg) daily x at least 6 months
- Dalteparin 200 iu/kg x 1 month, then 150 iu/kg x at least 5 months

Combined outcome of first recurrent VTE or major bleeding

- Edoxaban 12.8%
- Dalteparin 13.5%

Edoxaban pts experienced more bleeding events (6.9% vs 4.0%) than the dalteparin group

CAT – Treatment (LMWH vs DOACs) (2)

Select-D 2017

- Open-label, randomized, multicenter
- 406 cancer patients

- Dalteparin 200 iu/kg x 1 month, then 150 iu/kg x at least 5 months
- Rivaroxaban 15 mg bid x 21 days, then 20 mg daily for total x 6 months
- After 5 months of study medication, pts with index DVT underwent compression ultrasound of lower limbs.
- If U/S showed residual DVT or new PE, eligible to be randomly assigned to 6 months of rivaroxaban or placebo.

6 month VTE recurrence rate
- Rivaroxaban 4%
- Dalteparin 11%

Major bleeding
- Rivaroxaban 5.4%
- Dalteparin 3.0%

CRNMB
- Rivaroxaban 12.3%
- Dalteparin 3.0%

Young 2018

CAT – Treatment (LMWH vs DOACs)

- DOACs are at least as effective as LMWH for prevention of recurrent VTE, but increase the risk of major bleeding.

- More patients had major bleeding episodes on DOACs than on LMWH, most of these were upper GI bleeds, and most of these upper GI bleeds occurred in patients with GI cancers.

- Most clinically-relevant non-major bleeding occurred in rivaroxaban patients with GI or GU cancers.

Wang 2018

Rates of 6-month recurrent VTE, major bleeding and mortality in CLOT, CATCH, Hokusai VTE Cancer, Select-D

Study	CLOT		CATCH		Hokusai VTE Cancer		Select-D	
Arms	Warfarin	Dalteparin	Warfarin	Tinzaparin	Edoxaban	Dalteparin	Rivarox.	Dalteparin
Recurrent VTE	15.8%	8.0%	10.5%	6.9%	6.5%	8.8%	3.9%	8.9%
Major bleeding	3.6%	5.6%	2.4%	2.7%	5.6%	3.2%	5.4%	3.0%
Mortality	40.5%	38.7%	30.6%	33.4%	26.8%	24.2%	25.0%	30.0%

Wang 2018

Drug-drug interactions with DOACs

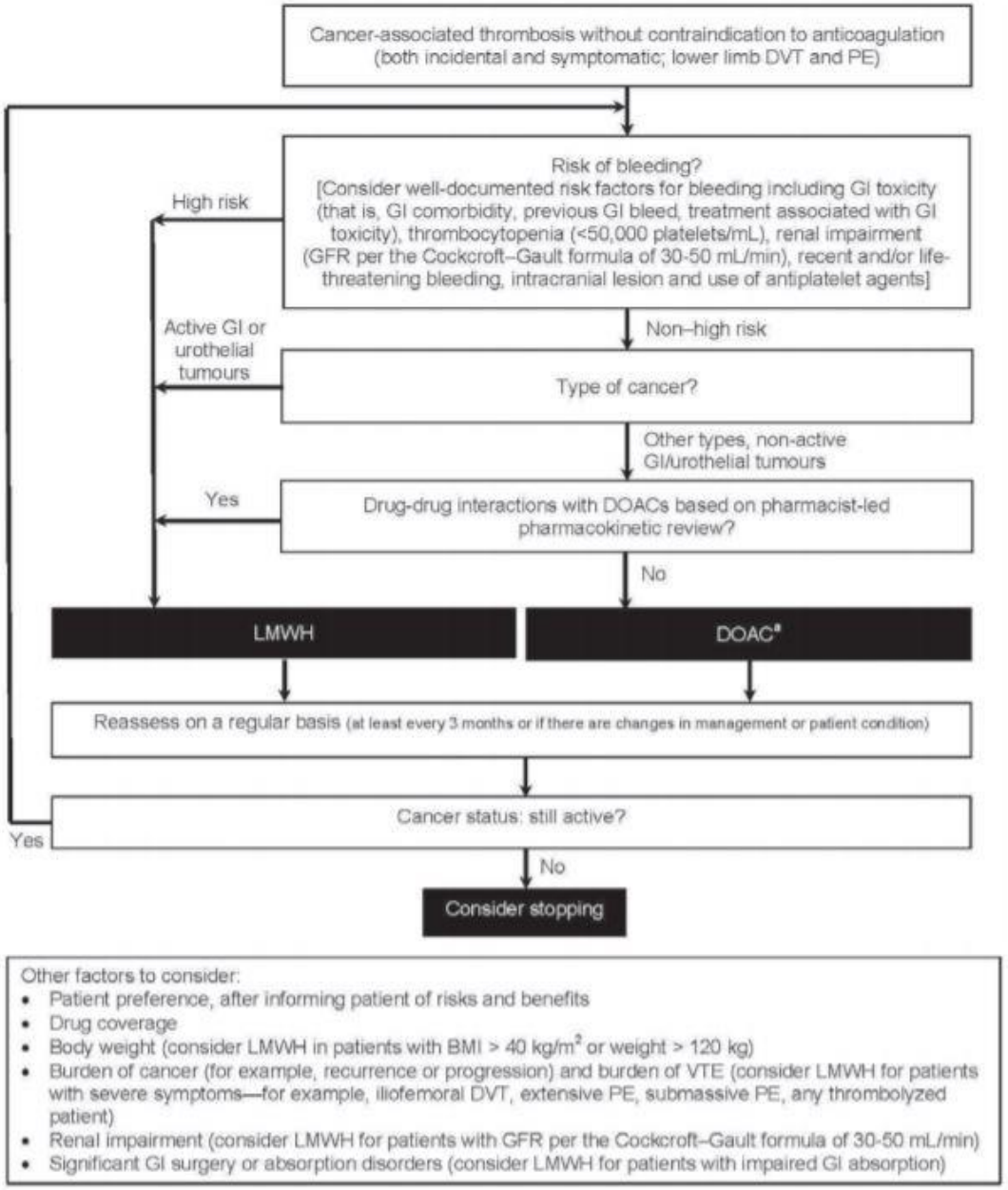
TABLE IV Common drug–drug interactions with direct factor Xa inhibitors[24–27]

Drug class and name	Interaction effect		
	Edoxaban[a]	Rivaroxaban[b]	Apixaban[b]
Antimitotic agents			
Vinblastine	↓	↓	↓
Anti-mycotic agents			
Azithromycin	↑	↑	↑
Clarithromycin	↑	↑	↑
Erythromycin	↑	↑	↑
Itroconazole	↑	↑	↑
Ketoconazole	↑	↑	↑
Posaconazole	—	↑	↑
Voriconazole	—	↑	↑
Anthracyclines			
Doxorubicin	↓	↓	↓
Hormonal agents			
Tamoxifen	↑	↑	↑
Immune-modulating agents			
Cyclosporine	↑	↑	↑
Dexamethasone	↓	↓	↓
Tacrolimus	↑	↑	↑
Protease inhibitors			
Indinavir	↑	↑	↑
Nelfinavir	↑	↑	↑
Ritonavir	↑	↑	↑
Saquinavir	↑	↑	↑
Tyrosine kinase inhibitors			
Imatinib	—	↓	↓
Lapatinib	↑	↑	↑
Nilotinib	↑	↑	↑
Sunitinib	↑	↑	↑

[a] Substrate of P-glycoprotein.
[b] Substrate of P-glycoprotein and CYP3A4 (cytochrome P450 3A4).
↑ = increases plasma factor Xa through P-glycoprotein or CYP3A4 inhibition; ↓ = decreases plasma factor Xa through P-glycoprotein or CYP3A4 induction; — = no effect on plasma factor Xa.

Carrier 2018

Canadian expert consensus Treatment Algorithm



Carrier 2018

Unanswered questions re: CAT Treatment

- Optimal duration of treatment (? beyond 6 months)
- Best choice of extended treatment beyond 6 months
- Recurrent VTE while on anticoagulation
- Patients experiencing bleeding, thrombocytopenia
- Patients with brain tumors → high thrombotic and bleeding risk
    - Metastatic brain tumor → AC not associated with increased risk of ICH
    - Glioma → 3.75-fold increased odds of ICH associated with enoxaparin

Wang 2018

Last thoughts ….

- These complications we have discussed today are commonly seen in the acute hospital setting in patients with known cancer diagnoses or new cancer patients that present with an oncologic emergency.
- Presentation may range from a slow and insidious onset to as rapidly as hours for some emergencies; a thorough work-up is imperative to obtain rapid diagnoses and initiate treatment.
- Symptoms may be non-specific → have a high index of suspicion.
- Pharmacists have a vital role on the Oncology team in recognizing and managing these patients.

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Questions?

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