



Memorial Sloan Kettering
Cancer Center

It's not just anthracyclines anymore!

What every ambulatory anesthesiologist should know about cancer treatment cardiotoxicities

Kara M. Barnett, MD, FASA

Memorial Sloan Kettering Cancer Center

Director of Anesthesia Services at MSK Monmouth

Stephanie Feldman, MD

Memorial Sloan Kettering Cancer Center

Cardio-Oncology Fellow



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Disclosures:

None





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Objectives:

- Identify potentially cardiotoxic chemotherapies in preoperative evaluation
- Recognize signs of cancer therapy related cardiotoxicity
- Discuss cardiac preoperative evaluation and periprocedural implications based on patient cancer treatment history

Background

- Cancer 2nd leading cause of death in the US
- Estimated 1.8 million new cancer cases in 2020
- Prior mainstay treatment cytotoxic chemotherapy + radiation + surgery now includes targeted and immune- based therapies
- More than 20 million cancer survivors in the US in 2020

Immune Checkpoint Inhibitors (ICI)

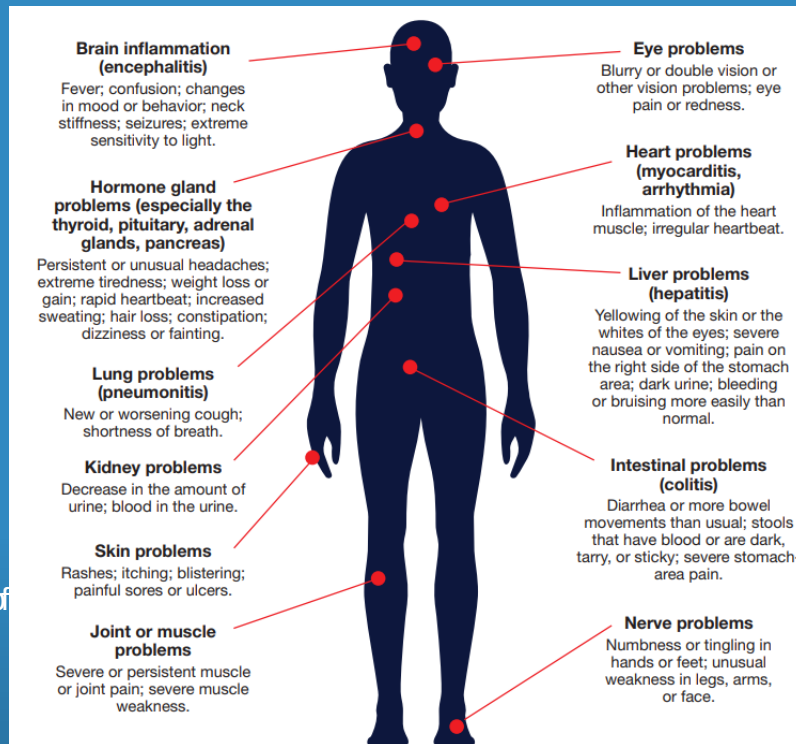
- Monoclonal antibodies that target immune system regulation receptors to target cancer cells
- 7 FDA approved ICI: ipilimumab, nivolumab, pembrolizumab, cemiplimab, avelumab, atezolizumab, and durvalumab
- Approved treatment of at least 18 cancers including: melanoma, renal cell carcinoma, colorectal, NSCLC, lymphomas

Immune Related Adverse Events (iRAEs)

Incidence:

Up to 35% (rash)

1-5% (colitis,
pneumonitis)



Cappell LC et al. Immune-Related Adverse Effects of Cancer Immunotherapy: Implications for Rheumatology. *Rheum Dis Clin North Am.* 2017;43(1):65-78.

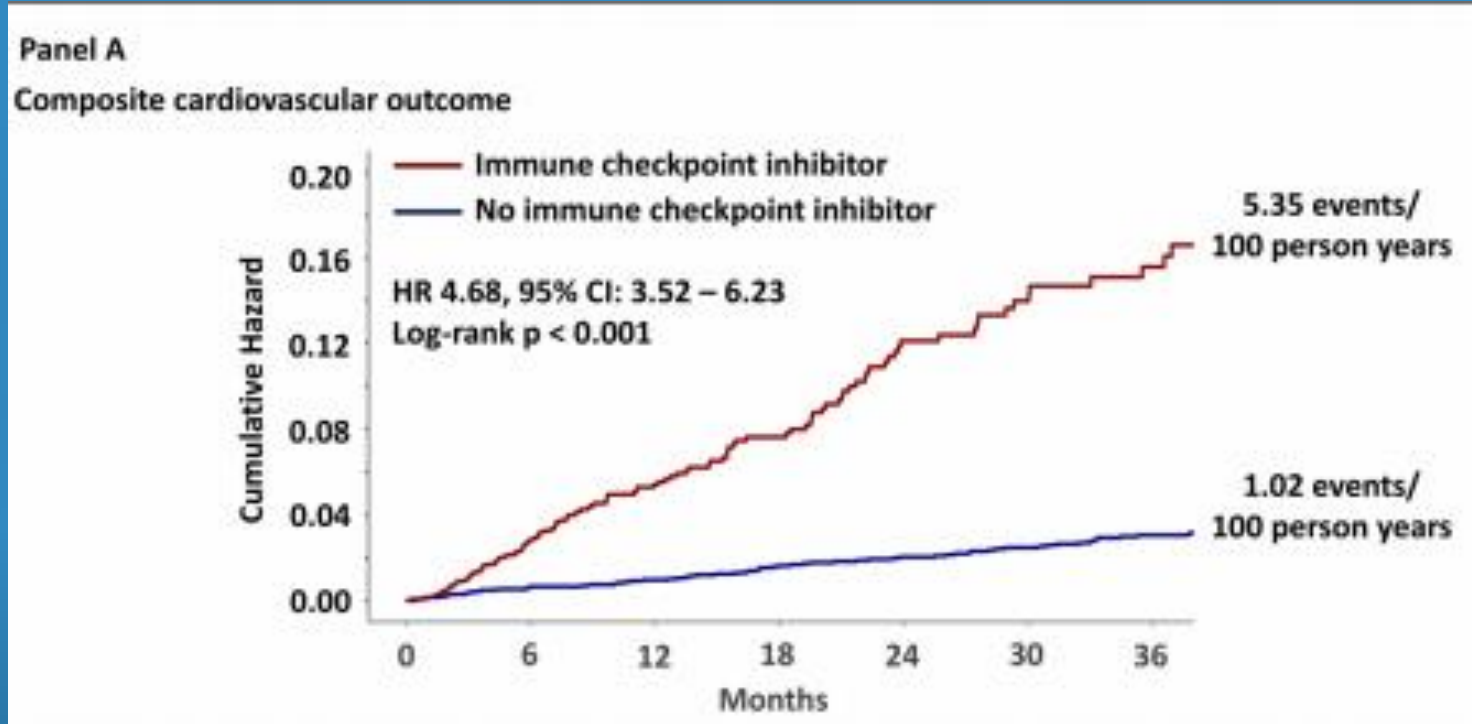
https://www.nccn.org/images/pdf/immunotherapy_infographic.pdf. Accessed 15 November 2020.

ICI Mediated Myocarditis

- Incidence 1-2.4%, mortality 38-46%
- Symptom onset most frequently within 2-3 months of treatment initiation
- Presentation non specific: fatigue, myalgia, chest pain, dyspnea
- Diagnosis: High level of suspicion, abnormal ECG, elevated troponin, atrial or ventricular arrhythmias, heart block, heart failure
- Treatment: **Medical emergency!** Immunosuppression

ICI and Adverse Cardiovascular Events

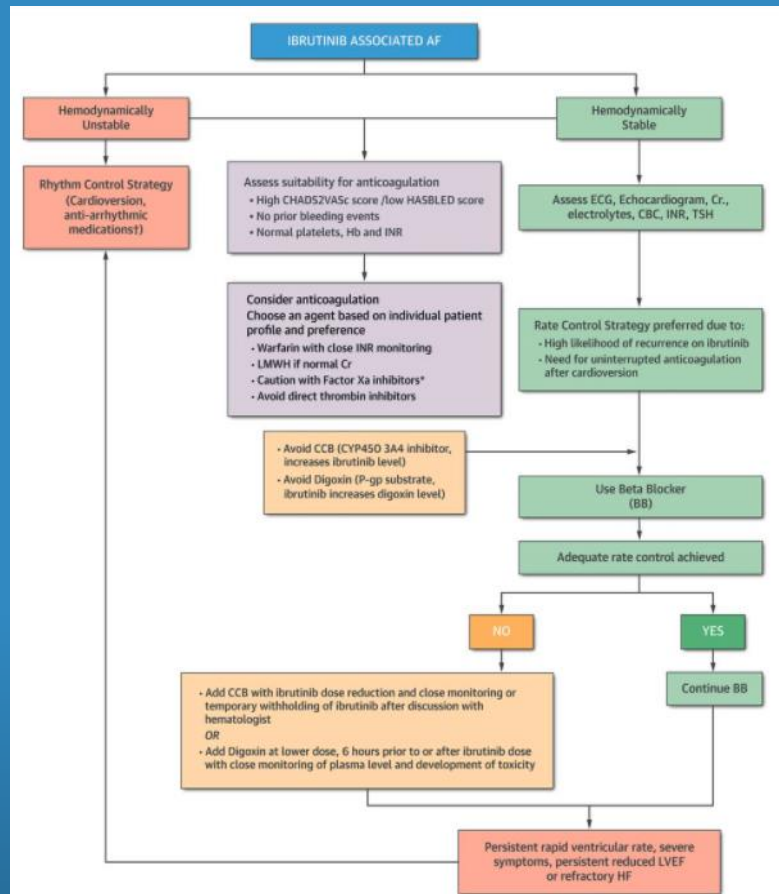
- ICI associated with threefold risk of cardiovascular events



Ibrutinib Related Atrial Fibrillation

- Ibrutinib: oral Bruton Tyrosine Kinase Inhibitor
- Used to treat: CLL, mantle cell lymphoma, Waldenstrom macroglobulinemia, marginal cell lymphoma
- Cardiac side effects: HTN, ventricular and atrial arrhythmias, excessive bleeding
- Incidence of atrial fibrillation 4-16%
- Management concerns: drug interactions, bleeding
- Should be stopped 7 days prior to surgery due to bleeding risk

Ibrutinib Related Atrial Fibrillation



5-FU Cardiotoxicity

- 5-FU and oral prodrug capecitabine inhibit enzyme involved in DNA replication
- Used to treat: solid tumors of glandular and squamous origin
- Cardiac side effects: coronary vasospasm, MI, CHF, arrhythmia, pericarditis, coronary artery dissection, QT prolongation
- Incidence of cardiotoxicity 1 to 19%
- Management: Stop 5-FU, CAD evaluation, aspirin, calcium channel blocker, nitrates

Cancer Therapies Associated with Myocardial Infarction/Ischemia

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/ Treatment
Antimetabolites			
Capecitabine	++++	3-9	Ischemia workup and treatment
Fluorouracil	++++	1-68	
Monoclonal antibody-based tyrosine kinase inhibitors			
Bevacizumab	+++	0.6-8.5	
Small molecule tyrosine kinase inhibitors			
Nilotinib	++++	5.0-9.4	
Ponatinib	+	12	
Angiogenesis inhibitors			
Lenalidomide	+++	0-1.9	
Antimicrotubule agents			
Paclitaxel	++++	<1.5	

Chemotherapy Related Hypertension

- Vascular endothelial growth factor (VEGF) inhibitors decrease NO production, angiogenesis → increased vascular resistance, fluid retention
- HTN reported in >50% patients on VEGF inhibitors
- Other mechanisms include thrombotic microangiopathy, nephrotoxicity
- HTN increases risk of CHF
- Rx: ACEi/ARB (if proteinuria), dihydropyridine CCB >> diuretics, chemo dose reduction/holiday

Cancer Therapies Associated with HTN

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Monoclonal antibody-based tyrosine kinase inhibitors			Pre-treatment risk assessment
Bevacizumab	+++	4-35	
Ado-trastuzumab emtansine	+	5.1	BP goal <140/90 mm Hg
Monoclonal antibodies			Weekly BP monitoring in 1st cycle
Alemtuzumab	+	14	
Ibritumomab	NA	7	Every 2-3 weeks BP monitoring for duration of therapy
Ofatumumab	+	5-8	
Rituximab	+++	6-12	
mTor inhibitors			Initiate BP treatment when diastolic BP increases by 20 mm Hg
Everolimus	++++	4-13	
Temsirolimus	++	7	

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Small molecule tyrosine kinase inhibitors			More than 1 anti-HTN medication may be needed
Pazopanib	++++	42	
Ponatinib	+	68	
Sorafenib	++++	7-43	Avoid diltiazem and verapamil with sorafenib
Sunitinib	++++	5-24	
Axitinib	++++	40	
Cabozantinib	NA	33-61	Hold chemotherapy as the last resort
Ibrutinib	++++	17	
Nilotinib	++++	10-11	Hold bevacizumab if systolic BP >160 mm Hg or diastolic BP >100 mm Hg
Ramucirumab	+	16	
Regorafenib	++++	30-59	
Trametinib	++++	15	
Vandetanib	NA	33	
Ziv-aflibercept	+	41	Early consultation with cardiologist
Proteasome inhibitors			
Bortezomib	++	6	
Carfilzomib	++	11-17	
Antimetabolites			
Decitabine	++	6	

Anthracycline + HER-2 Targeted Therapy Related Cardiomyopathy

- Anthracycline + trastuzumab/pertuzumab mainstay of treatment for HER2+ breast cancer
- Incidence asymptomatic LVEF decline 4-30%
- Anthracycline mediated cardiotoxicity is dose dependent, usually seen within 1 year (median 3 months)
- 4x risk of cardiac dysfunction with addition of trastuzumab

Cancer Therapies Associated with Heart Failure/ LV Dysfunction

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/Treatment
Anthracyclines			
Doxorubicin	++++	3-26	Monitor EF, GLS, troponin dexrazoxane, continuous infusion, liposomal preparation, BB/ACEI
Epirubicin	+	0.9-3.3	
Idarubicin	++	5-18	
Alkylating agents			
Cyclophosphamide	++++	7-28	
Ifosfamide	+++	17	
Antimetabolites			
Decitabine	++	5	
Clofarabine	+	27	
Antimicrotubule agents			
Docetaxel	++	2.3-8.0	

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/Treatment
Monoclonal antibody-based tyrosine kinase inhibitors			
Trastuzumab	+++	2-28	Avoid concomitant use with anthracyclines
Bevacizumab	++	1.0-10.9	
Adotrastuzumab emtansine	+	1.8	
Pertuzumab	+	0.9-16.0	
Small molecule tyrosine kinase inhibitors			
Pazopanib	++++	0.6-11.0	Treat hypertension aggressively Ischemia workup and treatment
Ponatinib	+	3-15	
Sorafenib	++++	1.9-11.0	
Dabrafenib	++++	8-9	
Sunitinib	++++	1-27	
Dasatinib	++++	8-9	
Lapatinib	++++	0.9-4.9	
Trametanib	++++	7-11	
Proteasome inhibitor			
Carfilzomib	++	7	
Bortezomib	++	2-5	

Chemotherapy Induced QT Prolongation

- Multiple classes of chemo agents impact cardiac repolarization → QT prolongation
- QT varies inversely with HR
- Friderica more accurate correction ($QT/RR^{1/3}$)
(<https://www.mdcalc.com/corrected-qt-interval-qtc>)
- Increased risk torsades de pointes with congenital LQT, antiemetics, some antibiotics, electrolyte abnormalities

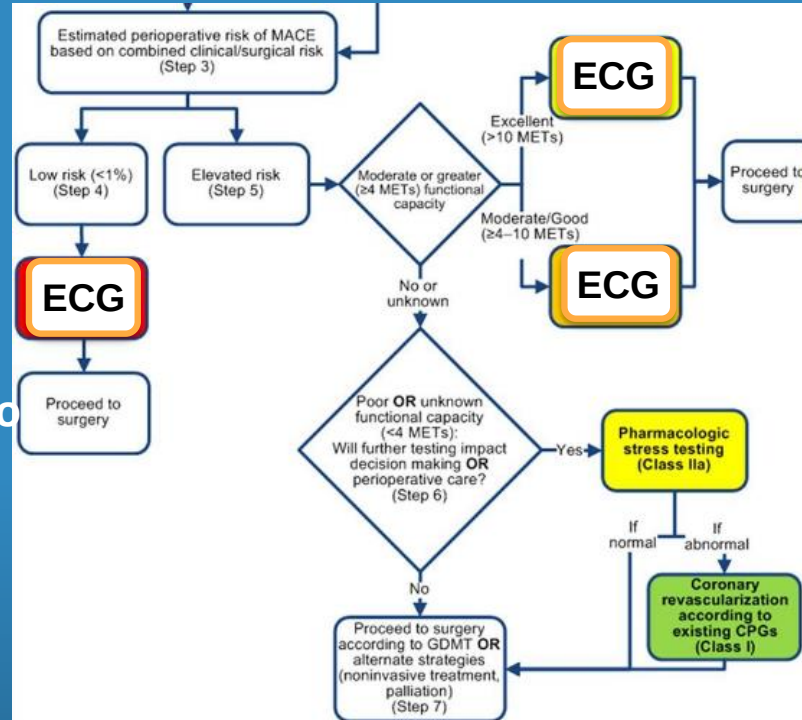
QT Prolonging Cancer Therapy

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Histone deacetylase inhibitors			Tangent method of QT measurement
Belinostat	+	4-11	
Vorinostat	++++	3.5-6.0	
Chemicals			Fridericia correction formula
Arsenic trioxide	++	26-93	
Small molecule tyrosine kinase inhibitors			Correct low K or Mg
Dabrafenib	++++	2-13	
Dasatinib	++++	<1-3	
Lapatinib	++++	10-16	
Nilotinib	++++	<1-10	
Vandetanib	++++	8-14	
BRAF inhibitor			QTc >500 ms or >60 ms above baseline associated with TdP
Vemurafenib	++++	3	
			TdP reported for arsenic trioxide, sunitinib, pazopanib, vandetanib, vemurafenib

Pre-operative Assessment of Patient with Cancer History

- **History**: Oncologic history, prior and current treatment, treatment complications
- **Medications**: Current chemo, supportive medications
- **Physical**: Attention to BP, HR, volume status
- **Prior Testing**: Recent ECG, Echo for monitoring?

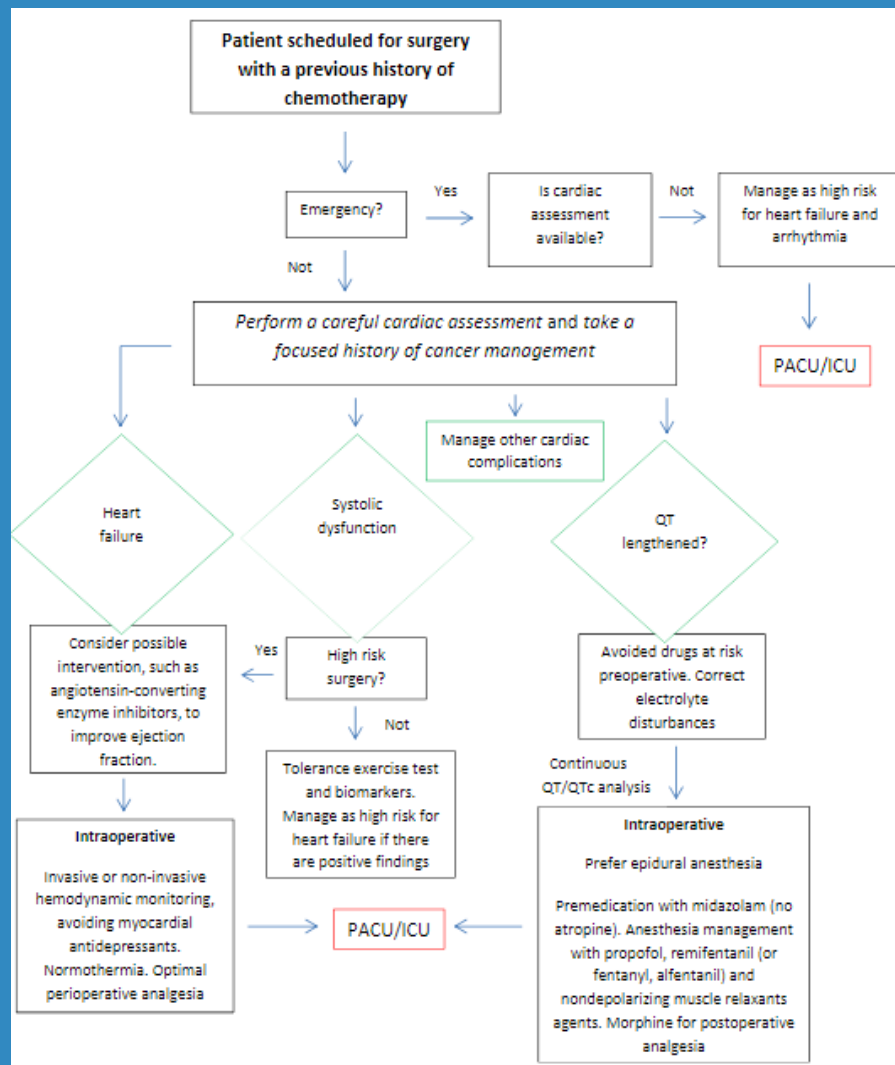
Pre-operative Assessment of Patient with Cancer History



*Consider if prior cardiotoxic
chemo, current cardiotoxic chemo

If ECG abnormal consider
TTE, cardiac evaluation

Feisher LA et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. J Am Coll Cardiol. 2014 Dec 9;64(22):e77-137.



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Take Home Points

- Many new cancer therapies with improved cancer prognosis as well as potential cardiac toxicities
- Pre-operative evaluation should include detailed cancer treatment history, active treatment, cardiac complications
- Drug interactions are common and can increase levels of chemo, increase bleeding risk, and increase risk of fatal arrhythmia

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