DEFINITION

• The care of patients with cancer with CV disease, overt or occult, whether already established or acquired during treatment
• Prevention, early recognition and mitigation of the effects of modern cancer treatment in the CV system
• Cancer survival has improved (23% decrease in cancer related death from 1991-2012) but toxicity has as well
• New therapies, especially TKI and immunotherapy are coming rapidly to market without full knowledge of side effects
It’s all about combination therapy
DEFINITION

• Cardiac toxicity includes HF, ischemia, arrhythmias, valvulopathies, pericarditis and fibrosis of valves, myocardium and pericardium
• Dedicated clinic, one stop (echo, CMR), preferably in conjunction with oncologist.
• We need risk scores, better diagnostic methodology, better treatment algorithms
• In the end improve QOL and actual survival
CARDIOTOXICITY

- Anthracyclines
- HER2/neu
- TKI’s
- ICI
- Proteasome inhibitors
- Alkylating agents
Current limitations of risk prediction

- There is a high degree of unexplained variability in tolerance to cardiotoxic treatment exposures.

Patient-Specific Risk Factors
- Age, HTN, LVEF/GLS, circulating biomarkers

Genetic Risk Factors
- Drug metabolism, drug transport, oxidative stress

Treatment-Related Risk Factors
- Anthracyclines, RT, anti-HER2 Rx

Subclinical Cardiotoxicity

Symptomatic Cardiotoxicity
CARDIOTOXICITY

- Cardiomyopathy: AC, HER2/neu
- Hypertension: VEGF inhibitors
- Thrombosis: BCR/Abl inhibitors
- Vasospasm: 5FU, Capecitabine
- Myocarditis: ICI
- Atrial fibrillation: Bruton’s kinase inhibitors
- QTc prolongation: Arsenic trioxide
HEART FAILURE

- Patients most at risk have defined CV risk factors and CV death is not uncommon
- Most common with AC, Tras, P.I and ICI but can HF can occur due to fluid overload, Stress induced cardiomyopathy or primary cancer invasion
- 1 to 5% of survivors develop a CIMP
- Definition: Clinical findings or decrease in LVEF
HEART FAILURE

• LVEF by echo, MUGA or CMR
• Echo: Use contrast. Temporal variability is 10% (3D only 6%)
• Strain: We estimate Global or Regional mechanical function
• TDI is user and angle dependent and does not differentiate translational or tethering artifacts
• Speckle tracking is angle independent and analyzes speckles within a 2D image with a specific algorithm which assess deformation. It predicts clinical decreases in LVEF months before they happen
• Drop of GLS under 19% or an 11% drop in original GLS is predictive
HEART FAILURE

• Biomarkers

• Troponin: Serial measurement in hematologic malignancies shows a correlation between increase and future EF drop. Persistent elevation deals a worse prognosis.

• BNP: The ventricles secrete biologically active BNP and inactive Pro BNP in response to an increase in ventricular volume or pressure overload. Only persistent elevation predicts HF
HEART FAILURE

• AC toxicity is dose related: 5% at 400 mg/m2
  16% at 500 mg/m2
  26% at 550 mg/m2

• However, sub clinical LV dysfunction at 180-240 mg/m2

• No safe dose but there is individual susceptibility

• Also toxicity can be acute (days to weeks) but mostly sub acute (months to years)
HEART FAILURE

- HER2/neu/ErbB is an over expressed signaling pathway in breast cancer. Present in 25% of cases.
- Inhibition of HER2 depresses pro survival pathways in cardiomyocytes and render them susceptible to injury.
- Mice deficient in HER2 develop a dilated CMP.
- Tras is a MAB against the HER2 TK with 33% decrease in mortality at one year in metastatic setting and 50% decrease in recurrence.
- Toxicity is 27% when given simultaneously with AC.
HEART FAILURE

- 4% CMP alone and 1% clinical HF. Other series 1.5 to 4% HF
- Follow EF and stop if absolute asx 10% EF or 5% sx drop to LT 55% 
- PERJETA and LAPATINIB no added or minimal toxicity
- Echo, MUGA, CMR and GLS
HEART FAILURE

• VEGF INHIBITORS ( VSP INH )
• Many agents with similar mechanism of action yet disparate side effects. Incidence of decrease in LVEF not clear
• Incidence of hypertension is 25-70% but also can cause CMP, cause conduction abn, ACS and arterial thrombosis
• Some block receptors that help the heart deal with stress so the heart is unable to deal with the hypertension
• Bevacizumab, Sorafenib, Sunitinib
HEART FAILURE

• PROTEASOME INHIBITORS
• Proteasome is a protein complex present in all cells and which degrades other proteins
• Its inhibition blocks cell proliferation leading to cancer cell apoptosis
• The proteasome plays a critical role in cardiomyocyte homeostasis
• Carfilzomib is an irreversible P.I. which causes new or worsening CHF or ischemia in 7% of patients (in a study of 266 pts 3.8 HF, 1.5% cardiac arrest and 0.8% MI). Toxicity is reversible with discontinuation
• Bortezomib is a reversible P.I and is safe
WHAT IS AMYLOIDOSIS?

- Amylum – starch (Latin)
- Protein misfolding disorder
# Cardiac Amyloid Subtype Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Precursor Protein</th>
<th>Pathophysiology</th>
<th>Cardiac Involvement</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (primary)</td>
<td>Light chain</td>
<td>Plasma cell disorder (bone marrow)</td>
<td>40-50%</td>
<td>Poor if untreated</td>
</tr>
<tr>
<td>Senile (SSA) Wild Type</td>
<td>TTR (Transthyretin)</td>
<td>Age related deposition</td>
<td>100%</td>
<td>5-7 years</td>
</tr>
<tr>
<td>Familiar (ATTR)</td>
<td>TTR</td>
<td>Mutant transthyretin</td>
<td>Mutation dependent</td>
<td>Variable</td>
</tr>
</tbody>
</table>
CARDIAC AMYLOIDOSIS: MANIFESTATIONS

• Heart failure
  – Diastolic dysfunction > systolic dysfunction
  – Predominant right heart failure symptoms
    • Peripheral edema and hepatomegaly

• Angina with normal coronaries
  – Amyloid infiltration of intramyocardial and microvessels

• Pre/syncope
  – Exertional syncope
  – Postural hypotension due to automatic neuropathy
  – Tachyarrhythmias
    • Atrial fibrillation/cardioembolic stroke

• AV block
AL AMYLOIDOSIS

- Most common type of amyloidosis diagnosed in US
- Rare disease but has incidence similar to Hodgkin’s lymphoma or CML
- 3,000-4,000 new cases per year in US, probably underdiagnosed with roughly 30,000 to 45,000 patients living with AL Amyloidosis
- Diagnosis often delayed due to multi-systemic presentations
- >1/3 of patients are diagnosed >1 year after the onset of symptoms; and after visits to multiple (≥5) specialists
- 25% patients present for treatment late in the course the disease with >2 major organ involvement

http://www.amyloidosis.org/facts
Banypersad et al, JAHA 2012
TTR CARDIAC AMYLOIDOSES

• Hereditary TTR
  – Caused by >100 delineated mutation in the TTR gene
  – Autosomal dominant inheritance; manifest with varying geographic distribution and phenotypic expression
  – In US, Val 122 Ile most common, found in 3.5% of the African-American population

• Wild type TTR
  – Common in the elderly population
  – Underdiagnosed and increasingly recognized cause of HFP EF:
    • ~20% HFP EF in the elderly population on autopsy
    • 13% HFP EF patients >60 years with IVS >1.2 cm showing positive TTR by technetium pyrophosphate scan with no TTR gene mutations.
CLUES TO DIAGNOSIS – WHEN TO SUSPECT CARDIOMYOPATHY WITH UNEXPLAINED “HYPERTROPHY ON ECHO”

• Typical Features:
  – Increased wall thickness with decreased LV end-diastolic volume
  – Granular/sparling appearance of the LV myocardium
  – Typically preserved or mildly reduced LV EF
  – Valve thickening and pericardial effusion
  – Increased right and left atrial volumes; reduced atrial function
  – Atrial septal thickening
  – RV thickening, reduced RV myocardial velocities
TTR AMYLOIDOSIS
TECHNETIUM PYROPHOSPHATE SCAN

HFpEF  AL Cardiac Amyloid  ATTR Cardiac Amyloid

Bokhari et al, Circ Cardiovasc Imaging 2013
CARDIAC AMYLOIDOSIS
MANAGEMENT OF CARDIAC RELATED SYMPTOMS

• Supportive Care
  – Diuretics mainstay/ salt restrictions
  – BB, ACEI and ARB may not be tolerated
  – Amiodarone safe to use atrial arrhythmia
  – Avoid calcium channel blockers/digoxin
  – Midodrine, Florinef for hypotension
  – Anticoagulate in AF regardless of CHADVASC score
  – Prophylactic PM or ICD use not associated with survival benefit
TREATMENT: TTR AMYLOIDOSIS

• Pharmacotherapy
  – Silencers – Suppression of TTR synthesis
    • siRNA, antisense oligonucleotides
  – TTR stabilizers
    • Diflunisal, Tafamidis*
  – Amyloid Fibril Degraders
    • Doxycycline/TUDCA
    • Anti-SAP antibodies

• Liver transplantation for familial TTR

*Recent FDA fast track designation after positive results of the Phase 3 ATTR-ACT
HEART FAILURE

- IMMUNE CHECKPOINT INHIBITORS
- Work by releasing inhibition of host immune receptors to cancer cells
- For decades Immunologists and Oncologists worked on this concept
- They were stymied as the inhibitory pathways CTLA-4, PD-1 and PDL-1 depressed the anti tumor function of T lymphocytes
HEART FAILURE

• Cancer cells exploit these pathways to escape tumor T cell specific mediated immunity
• ICI MAB work against CTLA-4 (Iplimumab), PD-1 (Nivolumab, Pembrolizumab) and PDL-1 (Atezolizumab, Avelumab and Durvalumab)
• Problem: they can cause an autoimmune myocarditis
• JACC: Registry of 35 patients
• More in those with risk factors (DM, combination therapy w TKIs)
HEART FAILURE

• Most <30 days. 81% at 3m. Prevalence was 1.14%
• Troponin abnormal in 94%. Higher worse prognosis ( >1.5 4x risk ).
• EF normal in 50% cases and normal EF meant little ( 40% of those with MACE had normal EF)
• MACE: CV death, cardiac arrest, CHB or card shock
• MACE was 46% ( much higher than for other myocarditis )
• Aggressive treatment with high dose steroids
HEART FAILURE

- With ICI 90% side effects manageable (low incidence of pneumonitis, hepatitis, diarrhea)
- For screening Echo and ECG not sensitive. Suggest troponin q2-3 weeks (infusion interval)
- Once sick LVEF dropped in 49%, ECG abn in 89%, BNP rose In 66% and Troponin abn in 94%
- Anti PD-1 most common, Nivo 0.6%, Pembro 1.3%.
• ANTI METABOLITES
  5 FU: Chest pain, MI, arrhythmia, HF and SDC
• Mechanism is vasospasm both endothelium independent and likely due to Protein kinase C mediated vasoconstriction of smooth muscle but also direct endothelial injury with microthrombotic lesions
• Sx last 48 h and can appear up to 5 days post infusion
• ECG changes in 68% with troponin elevation in 43% and mortality of 2.2-13%
CAD

- Predisposing factors: High dose
  - Continuous infusion (7.6%) v. bolus (2%)
  - RT, associated chemotherapy
- CAPECITABINE is the oral pro drug of 5FU, selectively activated in cancer cells with less toxicity (3-9%)
- Study of 644 patients only 5.2% had ECG changes and very rare troponin elevation
- We treat with nitrates and calcium channel blockers
HYPERTENSION

• Most common comorbidity in Cancer therapy: prevalence of 37%
• VSGF inh: incidence for Beva is 4-35% (1.7% severe enough for admission). Sora is 7-43%. Suni is 5-24%
• They decrease NO/Prostacycllin production and increase Endothelin-1 leading to vasoconstriction, increased PVR and hypertension
• Carfilzomib: In ENDEAVOR 17%. In ASPIRE 11%. Fatal in 2%.
• Causes endothelial dysfunction and decreases vasodilatation in response to ACC
HYPERTENSION

- Diagnosis: BP higher than 140/90 of two readings on two or more visits
- Preferred treatment are ACEi: they affect PAinh-1 and cause release of NO as well as decrease catabolism of bradikinin
- Avoid Cardizem and Verapamil with Sora (share Cyp450 metabolism through Cyp3A4 isoenzyme)
PERICARDIUM

- Late stage malignancies and affects about 5-15% of patients with cancer
- Lung, breast, leukemia and lymphoma
- Direct invasion, hematogenous or lymphatic spread
- Can also be due to RT, infectious or chemotx (AC, cyclophosphamide, Cytarabine, Imatinib, Dasatinib, Arsenic, less frequently Docetaxel and 5FU)
PERICARDIUM

- Tx is pericardiocentesis for tamponade, large effusions and diagnosis
- Poor prognosis: lung cancer, age over 65 and platelets <20k
- We keep the drain for 3-5 days until less than 50 cc/24h
- Surgical window if persistent but they will likely close
- Rarely IP Cisplatin or Bevacizumab
THROMBOEMBOLISM

- Cancer releases prothrombotic factors such as mucin, TF and cystein protease. They all activate the coagulation cascade.
- Usually early in the diagnosis (<6m).
- Increased incidence in lung, pancreas, colon, kidney, prostate and metastatic disease.
- Adjuvant chemotx, CVP lines, immobility, HF, AF.
20% of cancer patients develop VTE at some point during their illness
20% of VTE occurs in cancer patients
   – Heit, 2005; Prandoni et al, 2005; Hillen, 2000
Thrombosis in cancer is a property of aggressive disease, more than simply manifestation of “late stage”
DIFFICULTY USING WARFARIN FOR ANTICOAGULATION IN CANCER PATIENTS

• Unpredictable levels of anticoagulation
  – Drug interactions
  – Malnutrition / anorexia
  – Vomiting
  – Liver dysfunction

• Need for interruption of therapy
  – Invasive procedures
  – Chemotherapy-induced thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>Cancer</th>
<th>No Cancer</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Thrombosis</td>
<td>20.7%</td>
<td>6.8%</td>
<td>3.2</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>12.4%</td>
<td>4.9%</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Prandoni et al *Blood* 100:3484-3488, 2002
### POOLED ANALYSIS OF ANTICOAGULATION TRIALS IN CANCER ASSOCIATED THROMBOSIS

<table>
<thead>
<tr>
<th></th>
<th>Recurrent VTE (Events/At Risk)</th>
<th>Major Bleeding (Events/At Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>7.3% (62/846)</td>
<td>4.5% (42/925)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>12.4% (101/817)</td>
<td>4.0% (36/895)</td>
</tr>
</tbody>
</table>

- LMWH: Dalteparin, Enoxaparin, Tinzaparin
  - Lee et al, JAMA. 2015;314(7):677-686
TACHYARRHYTHMIAS

- SVT, AF and VT
- Breast, skin, prostate, colon and stage IV lung cancer (most common)
- Causes: Increased QTc, electrolyte abn ( n/v and diarrhea), direct tumor involvement and inflammation ( AF ), advanced age, pain and stress ( last 2 increase symp. drive), paraneoplastic syndromes targeting atria by an autoimmune process
- AF is bad: 4x increase in mortality after adjusting variables
TACHYARRHYTHMIAS

- Drugs associated with AF: 5FU, Cisplatin, AC, Pacli and Docetaxel, Ifosfamide, Gemtacitabine, Mitoxantrone, and IL2
- Ibrutinib (CLL, mantle cell lymphoma and Waldenstrom’s) causes both SVT/AF (3.5-10.8%) but also increased risk of bleeding. Targets Bruton’s TK and TEC PK impacting P13k-AKT signaling. The decreased activity of the latter promotes AF. Second generation Alacabrutininb does not cause AF (? More selective )
- SVT/AF: 8-10% incidence in BMT (more common with Melphalan in preconditioning chemotherapy)
- Tx: same as in non cancer but drug-drug interaction a problem as they share same Cyp450 metabolism or Glycoprotein mediated transport inhibition so chance of pro arrhythmia and QTc prolongation enhanced
Cancer and bleeding risk

H = Hypertension (>160)
A = Abnormal renal or liver function
S = Stroke
B = Bleeding
L = Labile INRs
E = “elderly” age > 65
D = Drugs or alcohol

<table>
<thead>
<tr>
<th>HAS-BLED</th>
<th>Bleed Rate/Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
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<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>--</td>
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<td>7</td>
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<tr>
<td>9</td>
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</tr>
</tbody>
</table>

- Specific cancers confer a marked increase in risk of hemorrhage
  - Primary or metastatic intracranial tumors
  - Hematologic malignancies
- Most patients with cancer will have HAS-BLED score of ≥3
  - Abnormal renal or liver function; drug; age

Farmakis et al., J Am Coll Cardiol 2014; 63: 945
RT

- Causes pericardial, epicardial, myocardial, microvascular and conduction system injury
- Consequence is valvulopathy, CAD, effusive constrictive pericarditis, tachy brady arrhythmias, HF (systolic and diastolic), autonomic dysfunction (increased HR and decrease HR recovery after exercise)
- Starts 5-10 years after exposure. Progressive and relentless
- EB RT increases risk