Cardiotoxicity of Cancer Therapy

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Late Mortality in Childhood Cancer Survivors

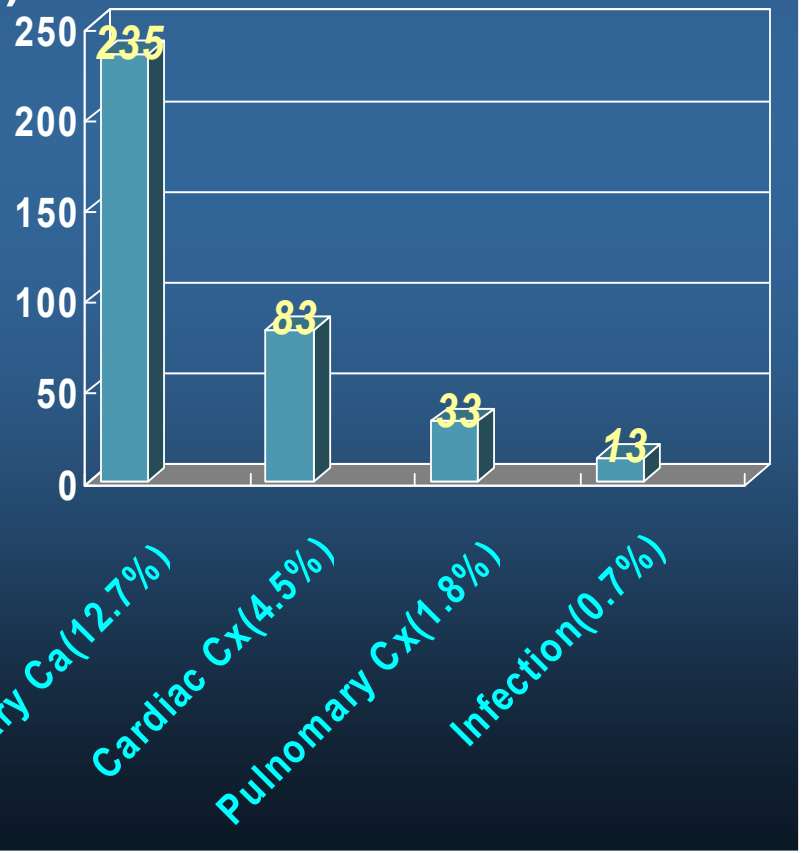
: The Childhood Cancer Survivor Study

- **Retrospective cohort of 20,227 5-year survivors** who was diagnosed from 1970 to 1986
- **Total mortality : 2030 Pts (10%)**

  Recurrence of Ca: 1,246 Pts (67.4%)

  Treatment-related consequences

  : 394 Pts (21.3%)



- **Absolute excess risk**
  (death per 1,000 person-years);

  Secondary cancers : 1.26

  Cardiac Cx : 0.27

  (Major causes : ACs, RTx)

  Pulmonary Cx : 0.015

Cause-Specific Standardized Mortality Ratio

	Subsequent Cancer*		Cardiac		Pulmonary		External Causes†		Other Deaths	
	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
All cases	19.4	17.2-21.8‡	8.2	6.4-10.4‡	9.2	6.5-12.5‡	0.8	0.7-1.0§	3.3	2.8-3.9‡
Sex										
Male	17.1	14.5-20.1‡	8.0	5.9-10.7‡	9.7	6.3-14.2‡	0.8	0.7-1.0	2.5	2.0-3.1‡
Female	22.5	18.9-26.6‡	8.7	5.5-13.0‡	8.5	4.7-13.9‡	0.7	0.4-1.1	5.2	4.0-6.6‡
Diagnosis										
Leukemia	17.4	13.3-22.2‡	3.8	1.5-7.6‡	8.2	4.1-16.3‡	0.6	0.4-0.9§	3.7	2.6-5.2‡
CNS	18.5	12.8-25.7‡	7.5	3.2-14.4‡	16.5	8.2-32.9‡	1.0	0.6-1.6	4.7	3.0-6.9‡
Hodgkin's disease	24.0	19.2-29.7‡	13.8	9.3-19.4‡	12.0	6.5-22.4‡	0.9	0.5-1.3	2.7	1.8-3.9‡
Non-Hodgkin's lymphoma	15.6	9.6-23.7‡	6.5	2.3-14.0‡	14.7	6.1-35.4‡	1.1	0.6-1.8	2.1	1.0-4.0§
Kidney (Wilms)	22.9	14.1-34.8‡	18.0	7.1-36.4‡	0.0	0.0-12.1	0.7	0.3-1.5	4.5	2.1-8.3‡
Neuroblastoma	12.6	5.7-23.4‡	8.4	1.4-25.8‡	0.0	0.0-16.0	1.2	0.5-2.4	2.3	0.6-5.9
Soft tissue sarcoma	19.5	13.3-27.3‡	5.7	2.0-12.2‡	7.3	2.4-22.6‡	0.5	0.2-1.0	3.7	2.2-5.8‡
Bone	18.5	12.6-25.9‡	4.9	1.8-10.5‡	4.7	1.2-18.6§	0.9	0.5-1.5	2.8	1.6-4.5‡

*Subsequent cancers included for survivor population. Cancer deaths resulting from progression of the original cancer are not included in the observed number of events.

†Includes accidents, homicides, and suicides.

‡$P < .01$ for SMR.

§$P < .05$ for SMR.

(Mertens AC et al. 2001)

Anthracyclines

- **Acute Cardiotoxicity**
  : from several hours to I wk
  Occur immediately after a single dose or course
  Uncommon (severe case <1%)
  Transient without longterm sequelae
  Abnormal ECG, arrhythmia, rarely pericarditis or LV failure
- **Early-onset Chronic Progressive Cardiotoxicity**
  : Within a year receiving ACs
  Common (incidence 1~16%), life threatening
  Decreased LVEF & CHF
  Related to cumulative dose
- **Late-onset Chronic Progressive Cardiotoxicity**
  : Several years or even decades after ACs (up to 20yrs)
  Ventricular dysfunction, CHF, arrhythmias
  More often in childhood/adolescence cancer survivors

Anthracyclines

- **Exact mechanism - unknown**

  : Formation of iron-dependent **oxygen free radicals**

  : Myocardium - **lower level of Enzymes detoxifying** oxygen free radicals compared with other tissues

  → **Irreversible damage to myocardial cell / Apoptosis**

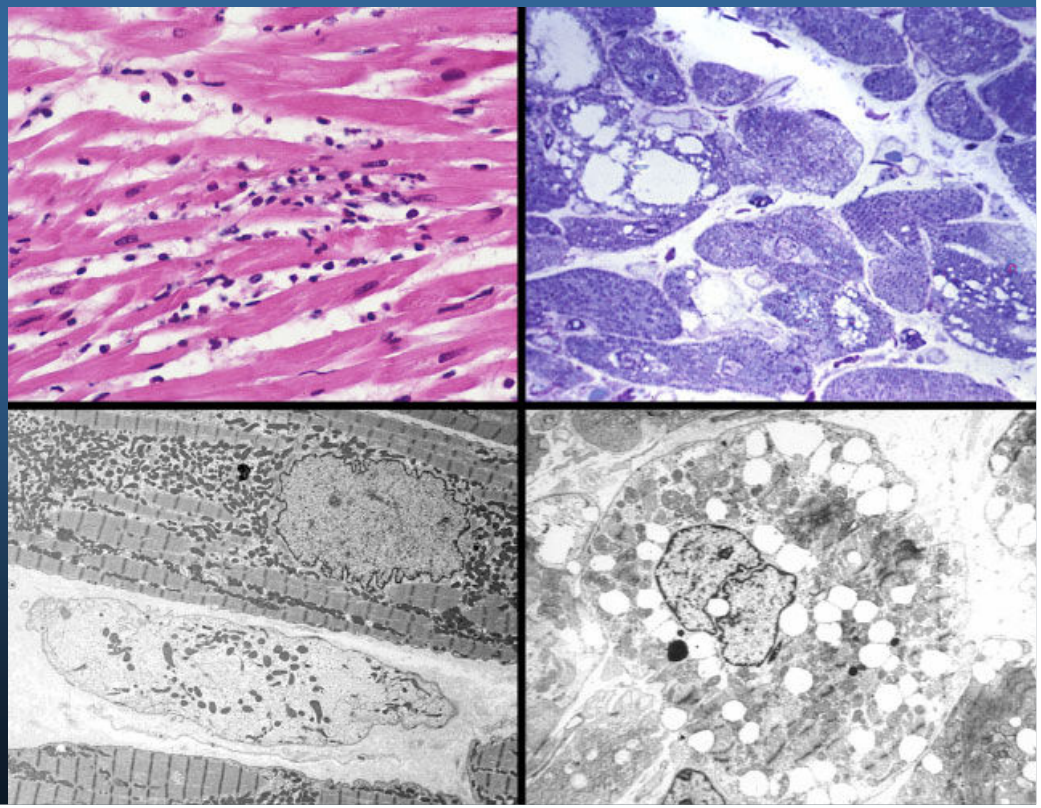
- **Pathologic changes :**

  Loss of myofibril in myocyte

  Vacuolization

  Mitochondrial degeneration

  Interstitial fibrosis



(Berry GJ et al. 2005)

Morphologic Grading of Chronic Anthracycline Cardiotoxicty

Grade	Morphology/clinical recommendations
0	Normal myocytes.
1	Isolated or scattered myocytes showing sarcotubular distension or early/partial myofibrillar loss; damage to <5% of all cells in Epon blocks.
1.5	similar to Grade 1.0 but involving 6%–15% of all cells in 10 plastic blocks.
2.0	Clusters of myocytes with myofibrillar loss or sarcotubular distension involving 16%–25% of all cells. →Therapy continued with close hemodynamic/cardiac assessment.
2.5	Numerous damaged myocytes (26%–35%) showing characterized changes. → One more dose of anthracycline.
3.0	Diffuse or confluent myocyte damage of >35% of cells. Necrotic cells may be seen. → Therapy is discontinued.

Risk Factors for Anthracycline Cardiotoxicity

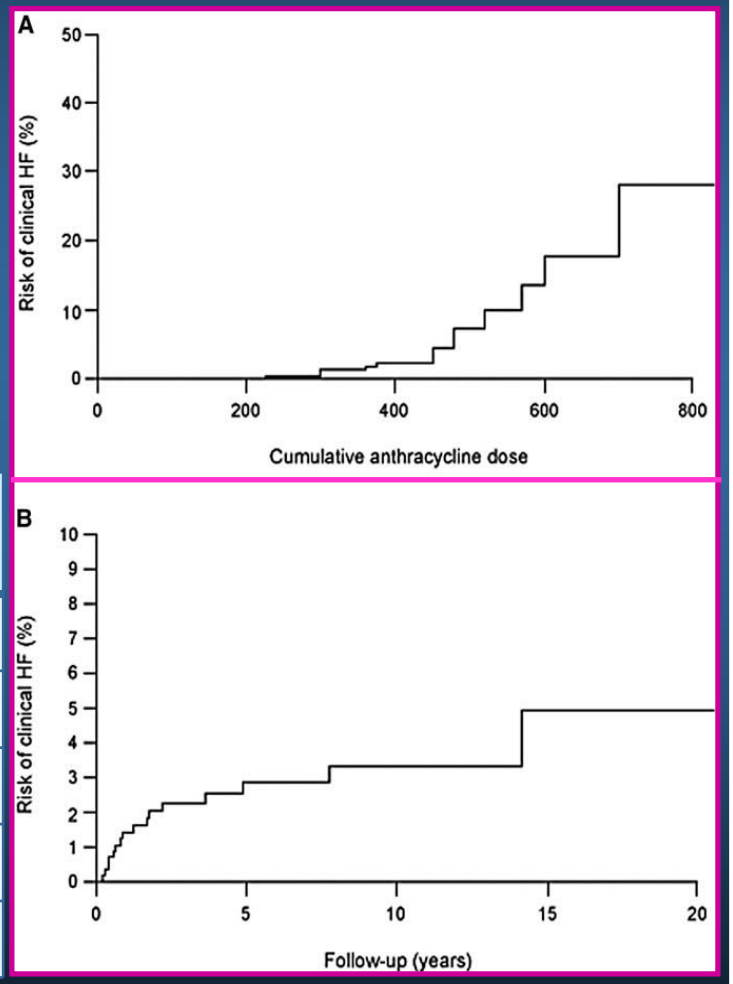
- **Patient-specific risk factors**
  - **Age > 65 or pediatrics**
    : Cardiac Cx in ≥60% children with high dose ACs
  - **Ionizing radiation to chest wall**
  - **Prior exposure to ACs**
  - **Preexisting cardiac disease or risk factors**
  - **Combination therapy : CYPH, MMC,VP16, MELP, VINC, BLEO**
  - **Marked interindividual variability**

- **CTx-specific risk factors**
  - **Dose of drug administered at each session**
  - **Type of ACs**
  - **Cumulative dose**
  - **Schedule of delivery : Continuous infusion vs IV bolus**

Cumulative Dose Related Anthracycline Cardiotoxicity

Cumulative Dose	incidence
400 mg/m2	< 5%
500 mg/m2	15%
550 mg/m2	25%
700 mg/m2	50%

Drug	Conversion factor	5% cardiotoxicity dose
Doxorubicin	1	450 mg/m2
Daunomycin	0.5	900 mg/m2
Epirubicin	0.5	935 mg/m2
Idarubicin	2.2	200 mg/m2
Mitoxantrone	2	225 mg/m2



(Lipshultz SE. 2006)

Prevention of Anthracycline Cardiotoxicity

- **Primary prevention**
  : Cumulative dose < 550mg/m2 → reduction in Tx efficacy
  : Continuous infusion (48~96h) rather than a bolus dose
- **Use of analogues**
  : Epirubicin, Idarubicin, Mitoxantrone
  - Lower propensity for cardiotoxic effects
  - Permitting higher dosages and a greater margin of safety

  ↔ Even at lower doses may cause subclinical cardiac injury
  ↔ Therapeutic efficacy is similar?
- **Alternative approaches to drug delivery**
  : Liposomal preparations- Doxil® (pegylated liposomal Doxo)
- **Cardioprotective agents : Dexrazoxane**

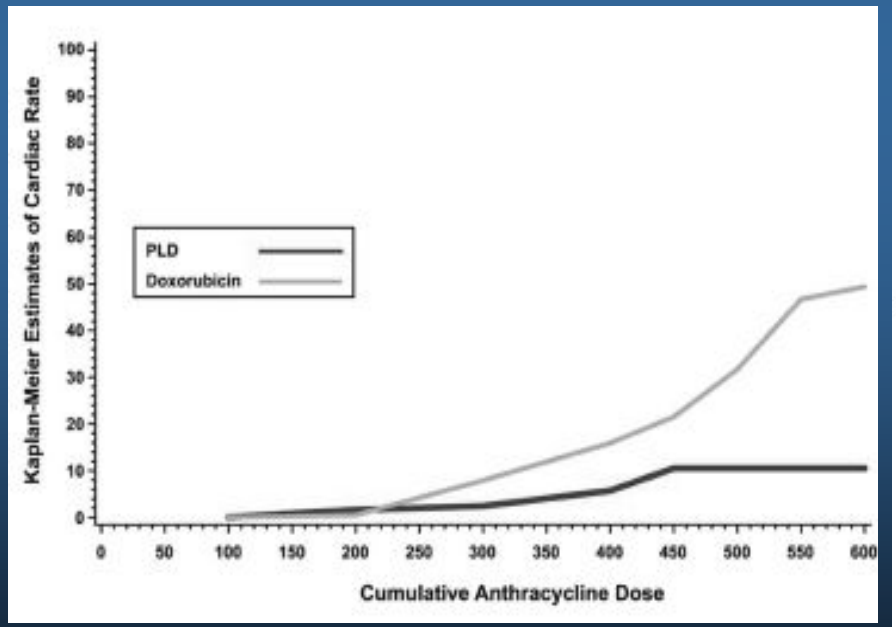
Prevention : Doxil®

- **Liposomal encapsulation → Cardiac sparing effect**

  : extravasate though leaky tumor vasculature

  : localize high concentrations directly at tumor sites

- **Phase III trial** in first-line treatment of metastatic breast cancer (MBC)



(O'brien ME et al. 2004)

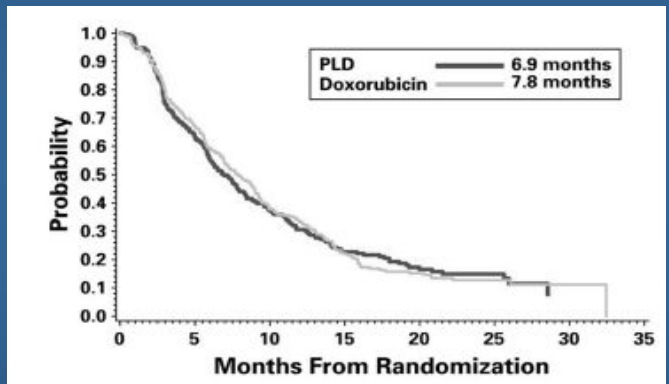


Figure 1. Progression-free survival [HR = 1.00 (95% CI for HR 0.82–

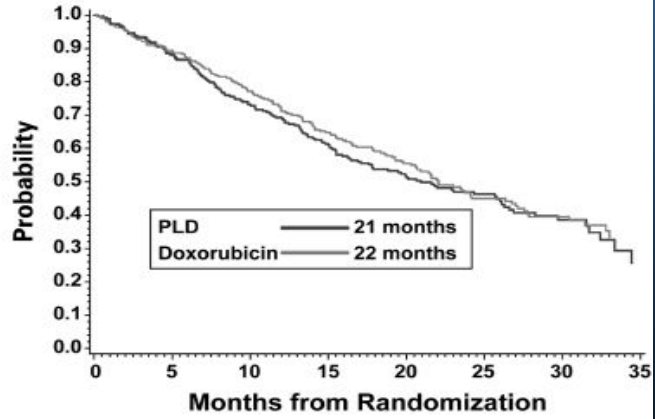
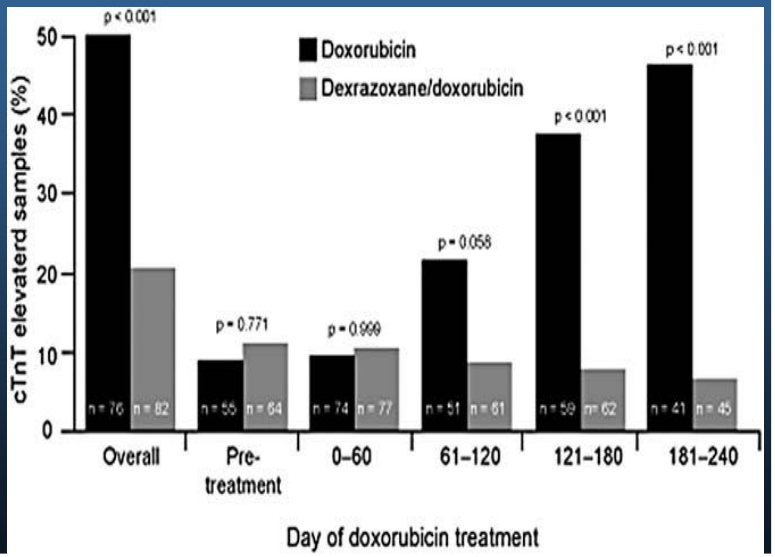


Figure 4. Overall survival [HR = 0.94 (95% CI for HR 0.74–1.19)].

Prevention : Dexrazoxane

- **Chemoprotectant**
  - : Prevent free radical formation as an intracelluar chelating agent
  - : Free iron & iron bound in ACs complexes
    - → decrease of ACs-induced free radical damage
  - : Indication in MBC ; > 300mg/m2 of DOXO
    - → decrease the relative risk of cardiomyopathy
  - : Pediatrics safety & efficacy not established
  - ↔ may decrease response rates
- **Side effect**
  - : myelosuppression
    - - significant leukopenia and/or thrombocytopenia in a few cases



(Lipshultz SE. 2006)

Monitoring

- Evidence-based guidelines yet to be established
- *Which method is optimal?*
  - P/Ex, EKG : Lack of specificity
  - Endomyocardial biopsy : Greatest reliability
    Invasive, Not completely safe
  - Echocardiography : High reliability & availability
  - Radionuclide ventriculography
    : High sensitivity for ischemia/ necrosis
    Low specificity
  - Biomarkers(Troponine I and T, BNP) : Useful for early diagnosis

- ACC/AHA/ASE 2003 Guideline for Clinical Application of Echo
  : Echo, Nuclear gated blood pool scanning - serially during Tx
  : Doppler-defined diastolic abnormalities
  - precede detectable systolic functional changes

Monitoring

- *How frequent monitoring?*
- ASCO(American Society of Clinical Oncology) Guidelines

: Baseline ECG & ECHO

: Consider repeating after

If Doxo < 300 mg/m2 : every 2 cycles

≥ 300 mg/m2 : every cycle

≥ 500 mg/m2 : every 50 mg/m2 of doxorubicin.

: Discontinuation; If LVEF decreases by 10% from baseline

decreases < 50% normal

<5% increase with exercise

If clinical CHF

: After CTx; at 3~6mo & 1yr, and after then, regular check-up

The 10 Commandment for Optimal Doppler-echo Scan of Oncologic Patients.

1. Quantify LV geometry (wall thickness, cavity diameters, relative wall thickness, LV mass).
2. Search regional wall motion abnormalities.
3. Estimate ejection fraction by 2D apical views if wall motion abnormalities are evident.
4. Analyze standard Doppler indexes of LV diastolic function.
5. Record pulsed Tissue Doppler of mitral annulus for detection of increasing LV filling pressure.
6. Explore structural and functional valve features, in particular mitral and aortic valves.
7. Visualize pericardium in all ultrasound views (including subcostal), particularly in patients at high risk (ACs, RTx).
8. Search ultrasound "comet tail" in patients at risk (ACs, RTx).
9. Scan carotids in patients treated by head and neck irradiation.
10. Perform stress echocardiography if coronary artery ds is suspected.

Treatment

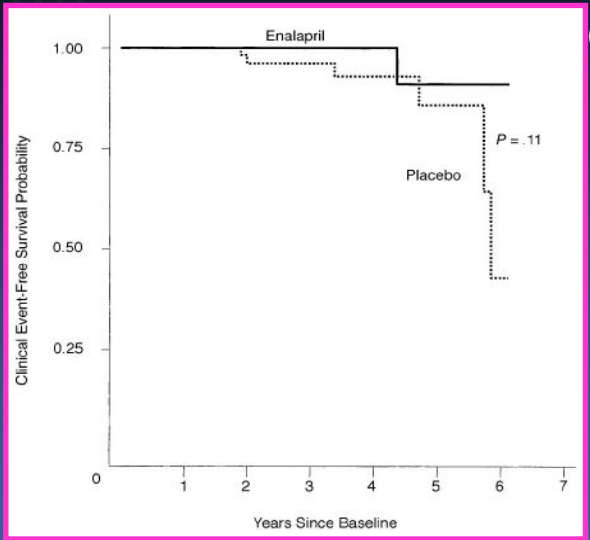
1. Conventional Tx : Diuretics, Digoxin, ACE inhibitor, β-blocker
   : show temporary response or refractory to Tx.
   : Pharmacologic intervention do not reverse CHF!!

- *ACE inhibitors:* Despite initial improvement, no long term benefit
  : Enalapril
  - In ASx LV dysfx, returned to pre-Tx levels of LV fx after 10 yrs
  - In HF, all Pts needed transplantation or died after 3-5yrs
- *β-blockers:* could delay the need for transplantation
  : Carvedilol
  - In case-control study, LVEF increased from 28% to 41%
  - In randomized trial,
    LVEF declined 17% in placebo & 1% in carvedilol group.
- *Growth hormone:* arresting progression of AC-induced CM

2. Heart Transplantation : only successful Tx option
3. Guideline for asymptomatic LV dysfunction/HF
   ACC/AHA/International Society for Heart & Lung Transplantation
   :Benefit of Tx in preventing ds progression in asymptomatic Pts.

(Lipshultz SE. 2006)

Enalapril



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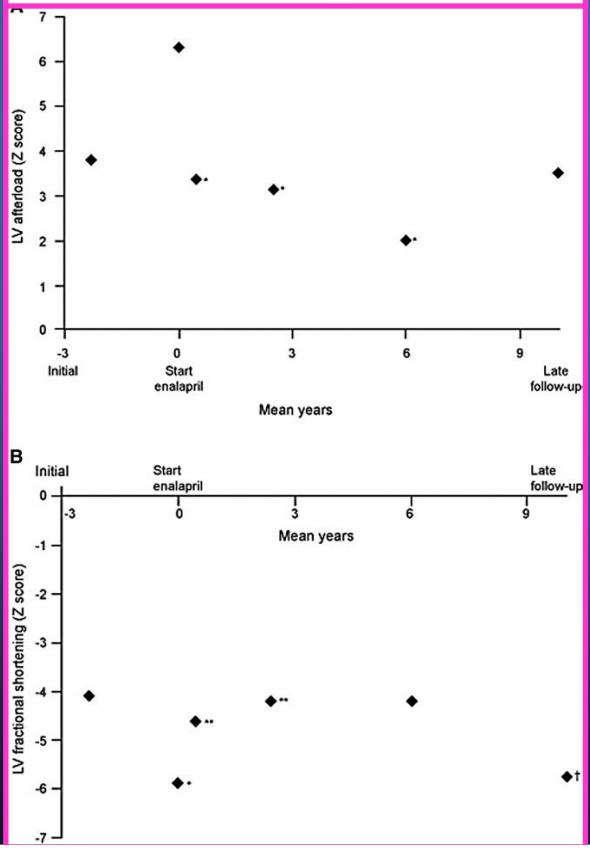
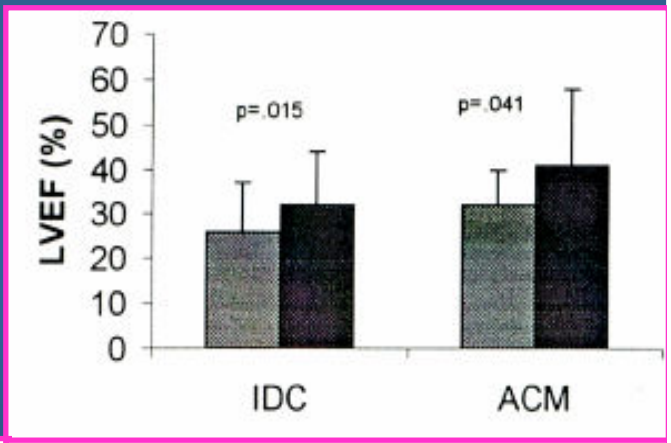
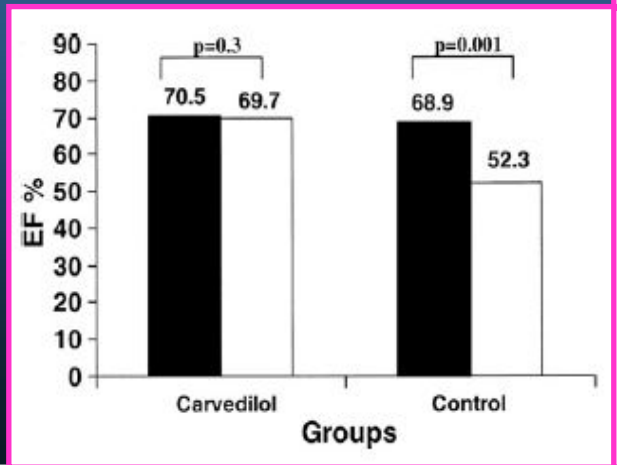
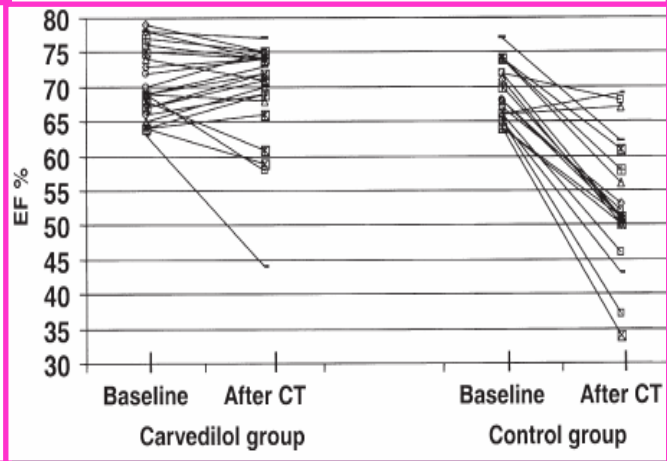
Carvedilol



(Kalay N et al. 2006)







Radiation Induced Heart Disease (RIHD)

- **Chest irradiation : 10-fold increased risk of cardiac deaths**
- **Incidence :**
  - **Cardiac exposure : Subcarinal block 2.5%**
    Partial cardiac shielding 7.5%
    Whole pericardial irradiation 20%
  - **Asymptomatic in many cases**
    : at more than 5yrs after RTx - 40% pericardial damage in echo
    - 5~10% clinically severe Ds
- **Onset of Sx : from days to more than 15yrs**
- **Risk factor : Total dosage (>35 Gy)**
  Volume of cardiac exposure
  Dose fractionation (>2.0 Gy/d)
  Concomitant CTx (esp. ACs)
  Preexisting CAD
  Young age

Spectrum of RIHD

1. Pericaridal disease - *Most Common*
   a. Acute fibrinous pericarditis during RTx
   b. Acute fibrinous pericarditis with delayed onset
   c. Constrictive pericarditis
2. Endocardial & myocardial disease
   a. Pancarditis
   b. Cardiomyopathy (Dilated, Hypertrophic, Restrictive CM)
   c. Endocardial fibrosis
3. Valvular disease
   Fibrosis with/without calcifications
4. Conduction disturbances
   Infranodal or atrioventricular nodal block
5. Coronary artery
   Arteriosclerosis/accelerated atherosclerosis

RIHD

1. Pericardial Disease

- **Acute fibrinous pericarditis**
  - : Early onset (during RTx) - likely caused by tumor lysis
  - : Delayed onset or chronic - spont. Resolution up to 2yrs
  - → *20% progress to constrictive pericarditis*
- **Constrictive pericarditis**
  - : can develop mos, yrs or decades after RTx
- **Tx:** Anti-inflammatory drugs, Pericardiocentesis, Pericardiectomy

2. Endocardial & myocardial disease

: Dose related (>3000rad)

: less common, more serious than pericardial ds.

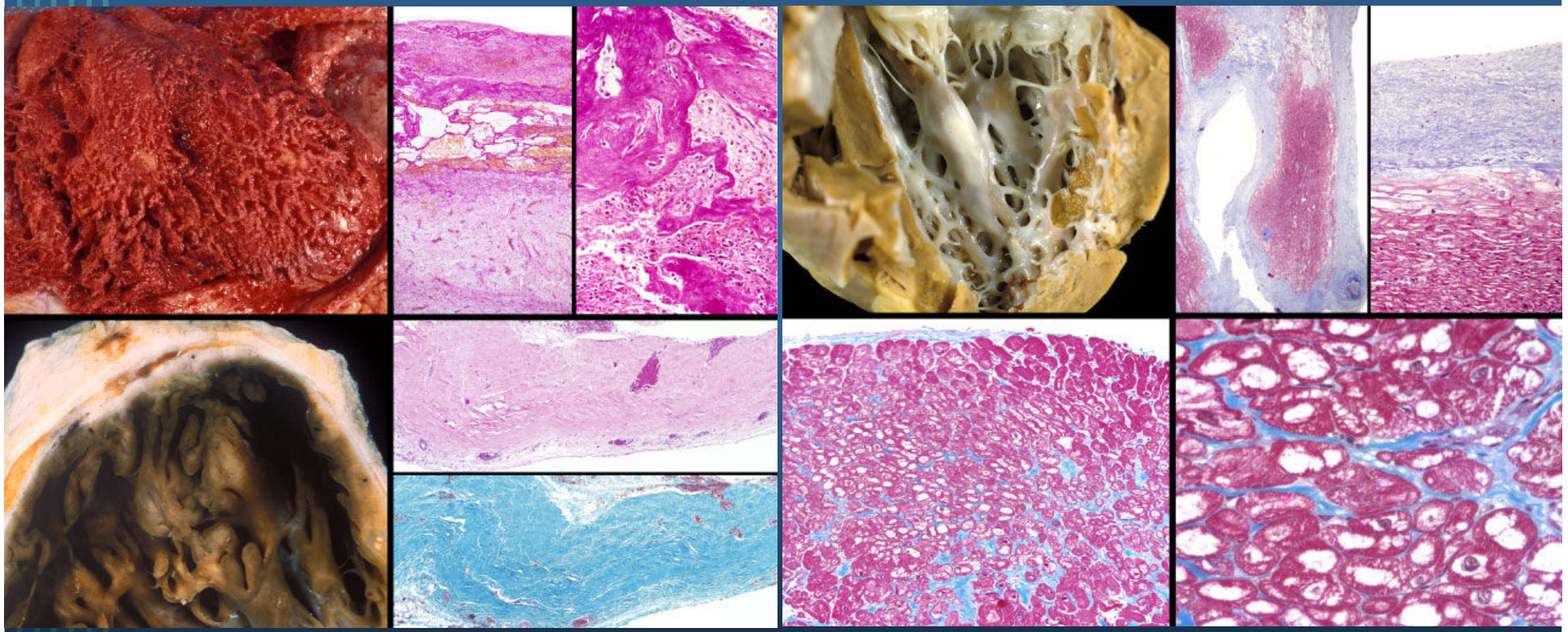
: Mechanism

- microvascular damage(esp. endothelial cell) with interstitial fibrous remodeling and myocardial ischemia.
- endocardial & myocardial fibrosis → resultant restrictive CM

3. Valvular disease

: Lt-sided valves more commonly affected and show regurgitant changes

Pericardial disease of RIHD	Cardiomyopathic type of RIHD



(Berry GJ et al. 2005)

Cardiotoxicity of Chemotherapeutic Agents

Drug	Toxicity	Incidence	Other information
Anthracyclines			
Doxorubicin Daunorubicin	CHF Cardiomyopathy	+++	
Alkylating agents			
Busulfan	Endocardial fibrosis Cardiac tamponade	+	4-9yrs after Tx Cumulative dose>600mg
Cisplatin	Ischemia, MI CHF Hypertension	++ ++ ++++	Very late onset : 10~20yrs after Tx CHF risk increase: elderly, after chest XRT, after prior ACs
Cyclophosphamide	Pericarditis Myocarditis CHF EKG changes	 + ++ +++	Incidence : 2~10% Acute cardiotocixity (last up to 6d) Hemorrhagic myocarditis ; rare RF: Total dose of individual course (>1.55g/m^2/d: 25%), elderly, after chest XRT, prior ACs Prevention: Fractionaing the dose into at least 2~3doses over 2~3days
Ifosfamide	CHF Arrhythmias	++ ++	RF: prior ACs, high cumulative dose (10~18g/m^2:17%), increased Cr level
Mitomycin	CHF	++	RF: high cumulative dose, prior ACs, after chest XRT

Antimetabolites			
Capecitabine	Ischemia	+	More common with CAD. by vasospasm or thrombosis
Cytarabine	Pericarditis CHF	+ 	Rare cases of cardiomyopathy /c cyclophosphamide
Fluorouracil	Ischemia (angina, MI) Cardiogenic shock ECG change	++ 	Reversible on cessation of 5-FU RF: CAD(risk x4), chest XRT, concomitant cisplatin
Antimicrotubules			
Paclitaxel	Arrhythmia Hypotension CHF	+ + ++	ASx.brady(76%),Heart block, PVC,VT Often seen with hypersensitivity possible if given with doxorubicin
Vinca alkaloids	Ischemia	++	RF:CAD, female, chest XRT
Monoclonal antibodies			
Trastuzumab	CHF/LV dysfunction	++	Her2 : critical role in embryonic cardiogenesis & cardiac hypertrophy Risk : monoTx -3~5% /c ACs & cyclophosphamide -27% Reversibility : 80% Pts respond to Tx
Alemtuzumab	Hypotension CHF	+++ +	In infusion reactions. rarely seen with mycosis fungoides.
Bevacizumab	Hypertension CHF	+++ ++	Severe HTN (200/110mmHg): 7% CHF: 14% with ACs

Miscellaneous			
IL-2 ·····	Hypotension Arrhythmias Thrombosis	++++ ++ +	Capillary leak sd (severe hypotension:3%)····· Prevent：premedication /c steroid
Interferon-α	Hypotension Ischemia	+++ ++	RF：preexisting cardiac dysfunction, prior cardiotoxic therapy
Asparaginase	MI Lipid abnormalities	+ ++++	Various effect on lipid profile: Decreases or increases in cholesterol and TGs
ATRA	CHF Hypotension Pericardial effusion	++ ++ +	In retinoic acid syndrome(26%, within 3wks): respiratory distress, fever, pulmonary edema, decrease LVEF(17%)
Arsenic trioxide	QT prolongation Torsade de pointes	++	Important to maintain normal electrolytes and to discontinue QT-prolonging drugs.
Imatinib	Pericardial effusion CHF Peripheral edema	++ +++	Severe fluid retention can rarely be fatal. Dose related, occurring in 50–70% of patients receiving 300mg/d.
Thalidomide	Peripheral edema DVT Bradycardia	++ ++ ++	Known severe congenital defects in fetuses. In multiple myeloma: routinely given low-dose warfarin for DVT prophylaxis.
Etoposide	Hypotension Ischemia	++ +	Coronary spasm by vasoactive substances RF: rapid infusion, c other CTx agents (many Pts /s cardiac RFs)

Cardiotoxic Syndromes Associated with Chemotherapeutic Agents

Cardiotoxic syndromes	Drugs
Myocardial depression	Anthracyclines Cyclophosphamide(Cytoxan) Trastuzumab(Hercentin) ATRA, Ifosfamide
Ischemia	5-FU Cisplatin, Capecitabine, Vinca alkaloids
Hypotension	Paclitaxel(Taxol) Etoposide, Rituximab(Rituxan), IL-2, IFN-α
Hypertension	Cisplatin, Bevacizumab
Bradyarrhythmias	Paclitaxel(Taxol), Thalidomide
Endocardial fibrosis	Busulfan
DVT	Thalidomide
Pericarcial or Pl. effusions	Imatinib(Glivec), Thalidomide

Time Course of Cardiotoxicity of Cancer Therapy

Acute (Anthracyclines, Cyclophosphamide, 5-FU, RTx)

1mo

Late (Anthracyclines, Cisplatin, RTx)

12mo 48mo

Very Late (RTx, Anthracyclines, Cisplatin)

48mo 144mo

The Duration of Cardiologic Monitoring *of Patients Undergoing Cancer Therapy Needs to be* ***Very Long and Accurate!!***