Anti-neoplastic Drugs and Cardiovascular Complications

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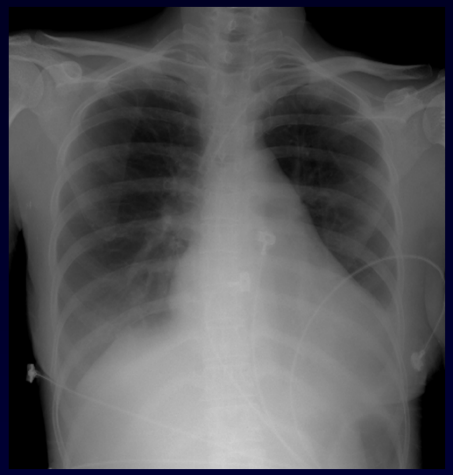
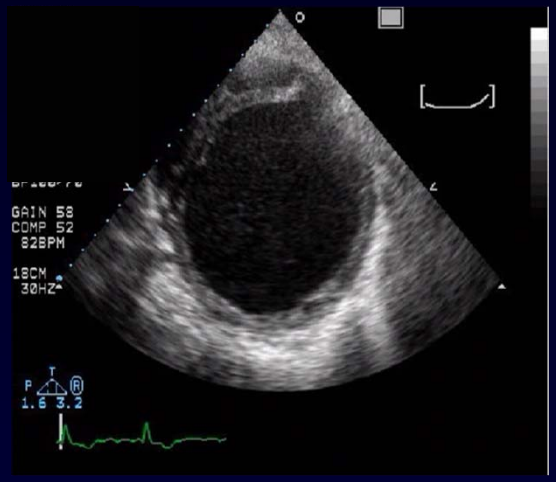
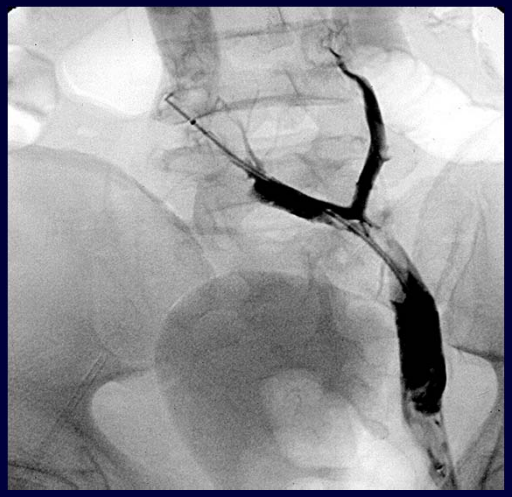
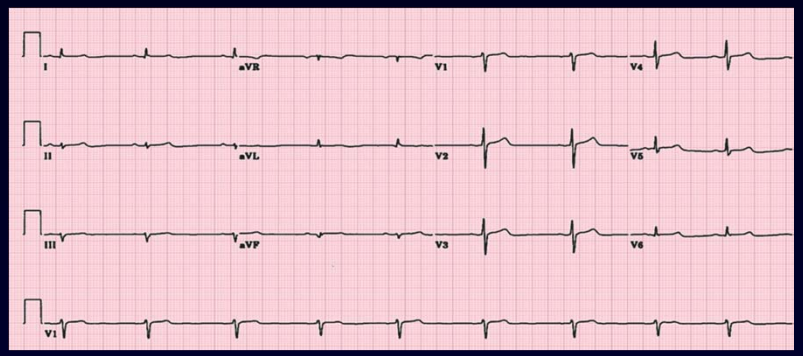
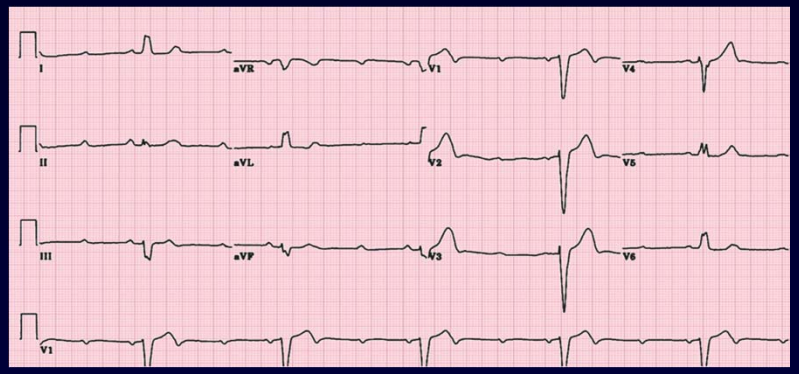
Cardiovascular Complications

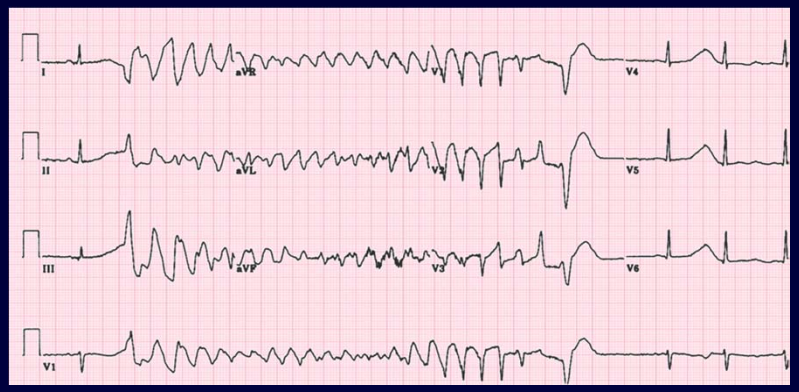












Chemotherapeutic agents-induced Cardiotoxicity

- Cardiomyopathy
- Arrhythmia : bradycardia, QT prolongation
- Myocardial ischemia
- Hypertension

CTx-associated with CMP

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3–26*	+++
Epirubicin (Ellence) (10)	0.9–3.3	++
Idarubicin (Idamycin PFS) (8)	5–18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11–13)	7–28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clolar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3–8	++
Monoclonal antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7–3	++
Trastuzumab (Herceptin) (20–28)	2–28	++
Proteasome inhibitor		
Bortezomib (Velcade) (10,17)	2–5	++
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	2–4	++
Imatinib mesylate (Gleevec) (34,35)	0.5–1.7	+
Lapatinib (Tykerb) (32)	1.5–2.2	+
Sunitinib (Sutent) (36,37)	2.7–11	+++

Frequency of Use

+++ : > 5000 doses/yr
++ : 1000-5000 doses/yr
+ : < 1000 doses/yr

Yeh ETH, et al. JACC, 2009;53:2231-47

Anthracyclin-induced CMP

- **Incidences**
  - Anthracycline medications are key component of treatment of many malignancies

  1) Acute (< 1%) : usually reversible
  2) Early onset chronic progressive : < 1 yr(1.6 – 2.1 %)
  3) Late onset chronic progressive (1.6 – 5 %)

- Dose - dependent

  : > 4% in 500-550 mg/m^2

  > 18% in 551-600 mg/m^2

  > 36% in > 601 mg/m^2

However,.....

No “safe“ maximal *dose* and *duration* !

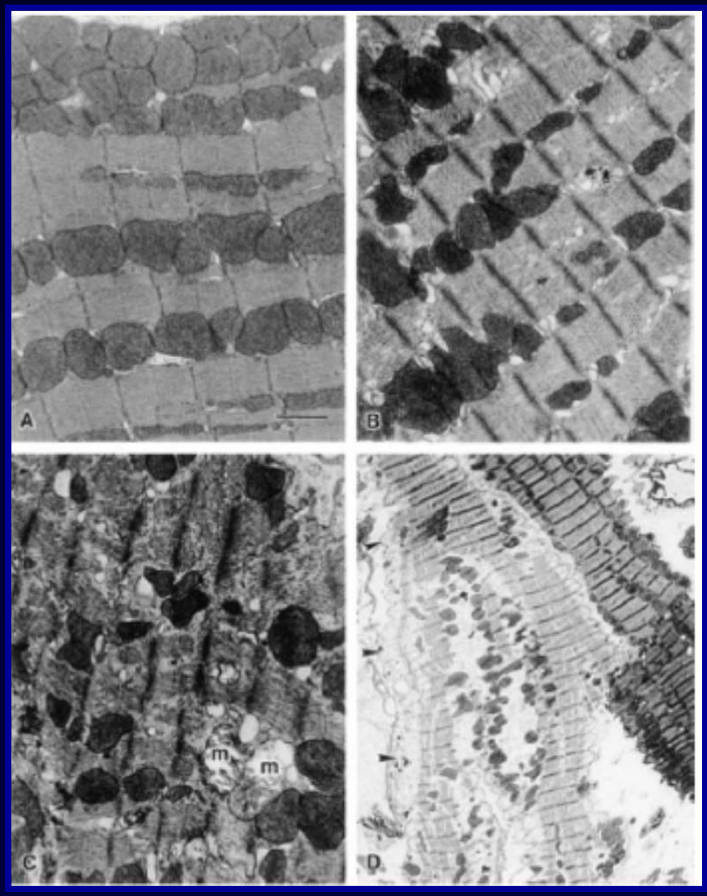
Anthracyclin-induced CMP

- **Risk factors**
  - Total cumulative dose : non-linear relationship
  - Age at the time of doxorubicin therapy (< 4 yrs, > 70 yrs)
  - Sex (female > male)
  - Mediastinal irradiation Hx.
  - Previous cardiac diseases
  - Trastuzumab or other cardiotoxic therapy
  - Duration since completion of therapy

Singal PK, et al, NEJM, 1998

Doxorubicin-induced CMP

- **Mechanisms : multifactorial**
  - Generation of free radicals
  - Reduction of antioxidants
  - Apoptosis
  - Lipid peroxidation
  - Interference with topoisomerase II beta
  - Downregulation of mRNA of SR calcium-ATPase



Zhou S, et al, Cancer Res, 2001

CTx-associated CMP

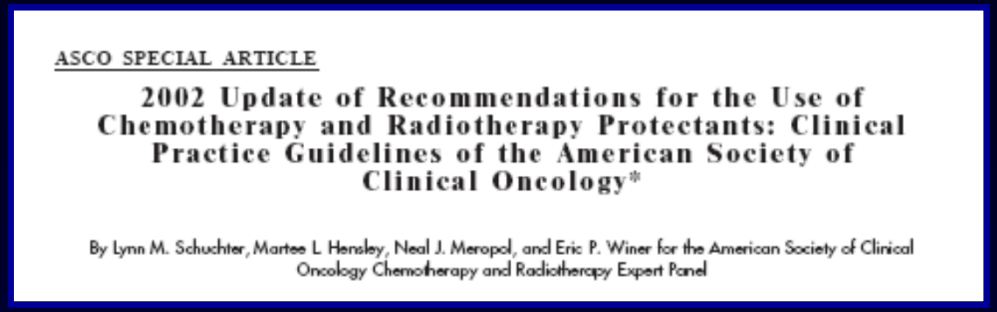
CTx agents	Mechanisms
Cyclophosphamide	• direct endothelial injury, • hemorrhage • intracapillary microemboli • coronary vasospasm
Bevacizumab(Avastin)	• uncontrolled HTN • inhibition of VEGF signaling
Trastuzumab(Herceptin)	• inhibition of ErbB2 signaling • immune-mediated
Bortezomib(Velcade)	• proteosome inhibition

Yeh ETH, et al. JACC, 2009;53:2231-47

Therefore,
cardiologic screening and follow-up *before* and *during* as well as *after* therapy
is advised for pts during chemotherapy

Doxorubicin-associated CMP

- **Prevention**
- **ASCO guideline**



ASCO SPECIAL ARTICLE

2002 Update of Recommendations for the Use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology*

By Lynn M. Schuchter, Martee L. Hensley, Neal J. Meropol, and Eric P. Winer for the American Society of Clinical Oncology Chemotherapy and Radiotherapy Expert Panel

- **Cardiac monitoring after cumulative dose of 400 mg/m^2**
- **Repeat after 500 mg/m^2 and then, after every 50 mg/m^2**

However,
No describe a method to monitor cardiac function
No specific time interval

Doxorubicin-induced CMP

- **AHA/ACC guideline**

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)

- Pts. treated with anthracyclines be monitored closely for cardiotoxicity development

- **ASNC and ASE guideline**
- Recommend the use of radionuclide angiocardiography (RNA) : baseline and repeat when indicated
- Echocardiography : baseline and continued monitoring of EF throughout the course of chemotherapy

Questions not answered for anthracycline induced cardiotoxicity

- What is the predictive value of cardiac function monitoring during anthracycline therapy ?
- When should baseline cardiac function be monitored ?
- Should all patients receiving anthracyclines follow the same monitoring schedule?

Table 1. Early Cardiac Decline and the Development of Long-Term Cardiac Dysfunction

Reference	Design	Monitoring	Results
Correlation between early cardiac decline and late cardiotoxicity			
Steinherz (1991)[1]	retrospective/prospective; ≥200 mg/m² doxorubicin or daunorubicin; N = 78	ECHO: end of therapy (early—retrospective), 4–20 y after treatment (late—prospective)	normal early ECHO normal late ECHO 88%, abnormal late ECHO 12%[a] abnormal early ECHO normal late ECHO 29%, abnormal late ECHO 71%[a]
Nousiainen (2002)[17]	prospective; ≥400 mg/m² doxorubicin; N = 28	RNV: baseline, 200, 400, and 500 mg/m²	decrease >4% in LVEF at 200 mg/m² positive predictive value 64% decrease <4% in LVEF at 200 mg/m² negative predictive value 93%
Belham (2007)[18]	prospective; doxorubicin; N = 67	ECHO: baseline, midpoint, end of therapy	decrease >4% in LVEF at midpoint positive predictive value 67% decrease <4% in LVEF at midpoint negative predictive value 96%
No correlation between early cardiac decline and late cardiotoxicity			
Meinardi (2001)[19]	prospective; ≥360 mg/m² epirubicin; N = 40	ECHO: baseline, 1 mo after end of therapy, 1 mo after completing radiotherapy, 1 y after starting chemotherapy RNV: baseline, 1 year after starting chemotherapy	early changes in ECHO were not correlated with changes in RNV from baseline to 1 y after starting chemotherapy
Jensen (2002)[20]	prospective, blinded; 1000 mg/m² epirubicin; N = 85	RNA: baseline, 500, 780, 900, and 1000 mg/m² and 1, 3, 6, and 33 mo after end of therapy	no significant decline in LVEF during therapy

ECHO = echocardiogram; LVEF = left ventricular ejection fraction; RNA = radionuclide angiocardiography; RNV = radionuclide ventriculography.
[a]$p < 0.001$.

Jannazzo A, et al, Ann Pharmacother, 20

CTx-associated CMP

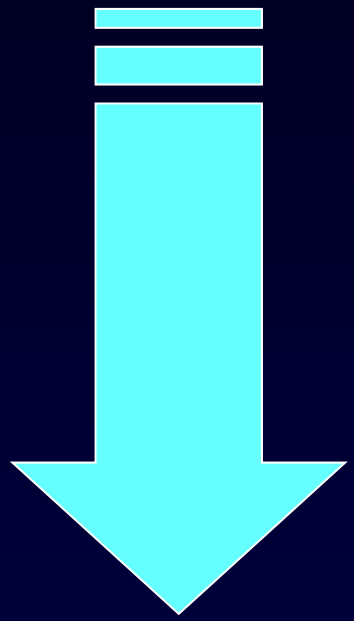
- **Monitoring**
  - Endomyocardial biopsy
  - Echocardiography : EF, E/A,..
  - Radionuclide angiocardiography (RNA)
  - Molecular cardiac imaging
    - Neuronal imaging : ^{123}I-MIBG
    - Imaging necrosis
    - Imaging apoptosis
  - Biomarkers : cTnT, BNP(diastolic > systolic), …

Biomarkers

- Cardiac troponins (cTnT, cTnI)
- ANP
- BNP/NT-proBNP
- Ischemia modified albumin(IMA)
- Lipid peroxide
- CPK, LDH

Noninvasive, not expensive, easily analyzed, quantitative assessment of cardiac damage

Effective biomarkers of acute cardiac damage during CTx



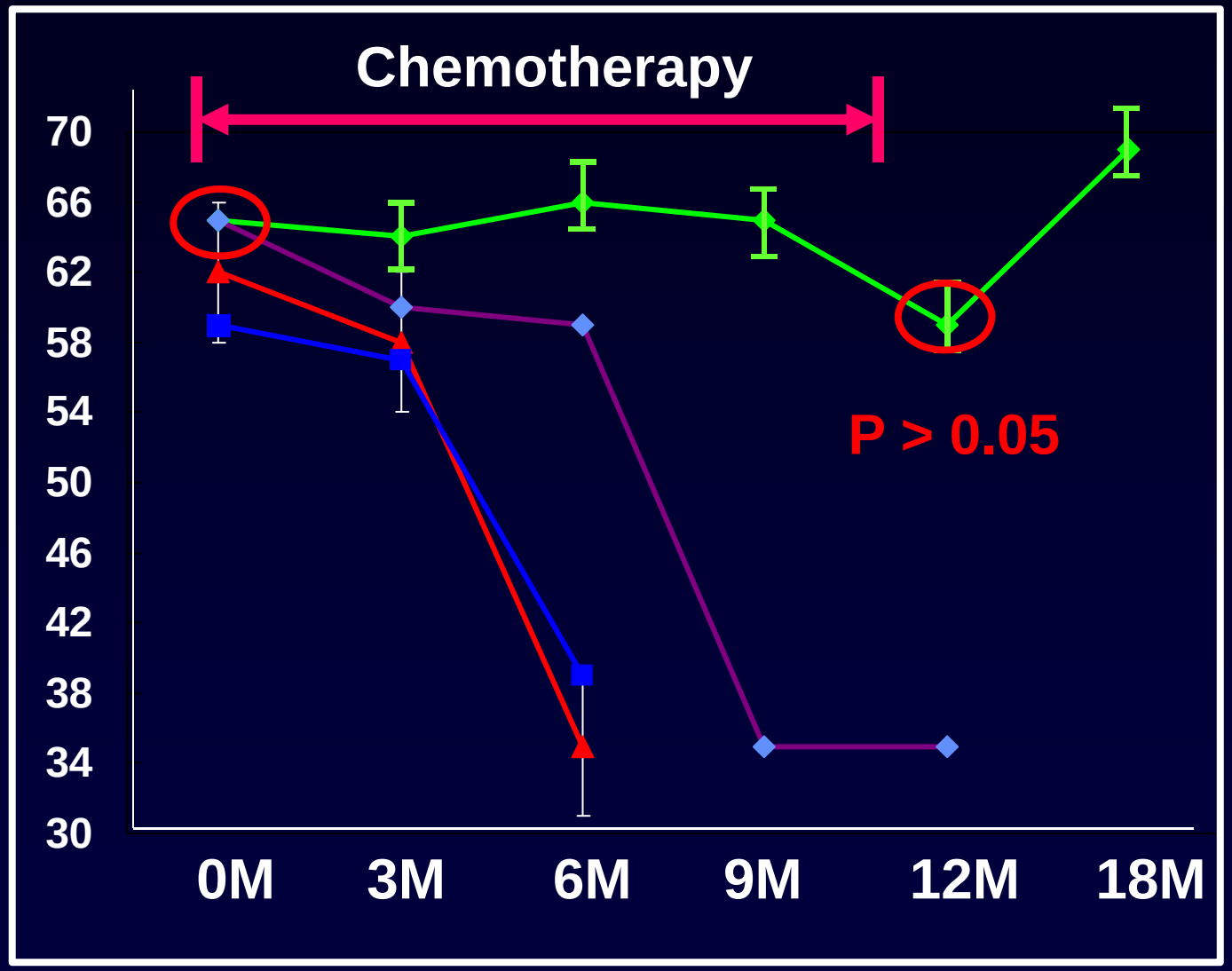
Predict long-term cardiac outcomes and allow modification of treatment protocol during CTx

Problems

- Timing of blood sample ?
- Various cumulative anthracycline dose
- Inadequate sample size
- Short study duration
- Different age of study groups

The evidence is limited not only in quantity but also quality

Change of LV ejection fraction



N=22 pts

Average EF

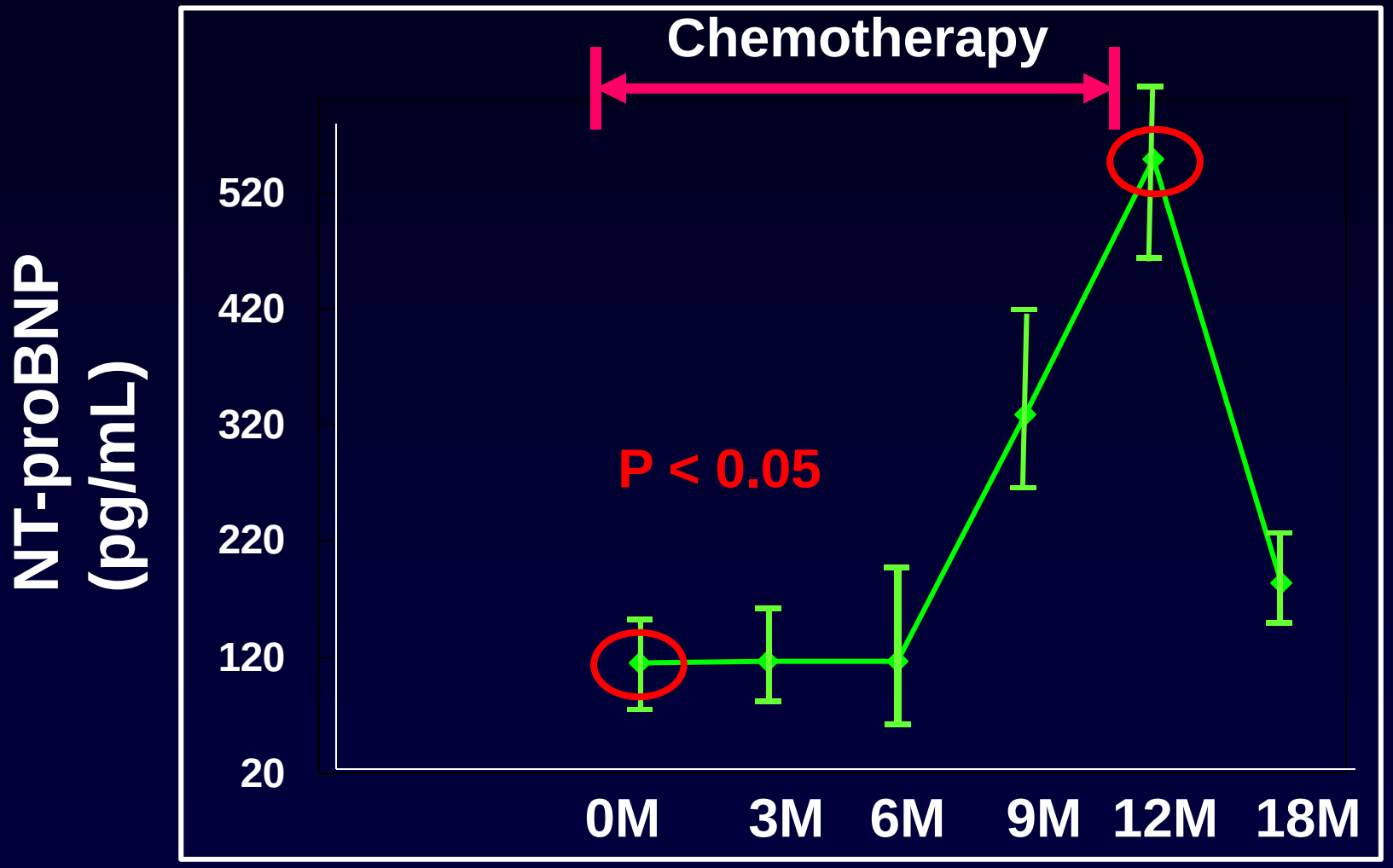
ADR cardiomyopathy
(3 cases)

: 1 case
: 2 case
: 3 case

Average cummulative adriamycin dose(mg/m^2)
: 409 ± 97.2

Kang SM, et al, ASE abstract, 2003

Change of NT-proBNP



Kang SM, et al, ASE abstract, 2003

Yonsei Medical Journal
Vol. 46, No. 1, pp. 73 - 77, 2005

Serial Assessment of Myocardial Properties Using Cyclic Variation of Integrated Backscatter in an Adriamycin-Induced Cardiomyopathy Rat Model

Jong-Won Ha[1], Seok-Min Kang[1], Wook-Bum Pyun[1], Joo-Yong Lee[1], Mi-Young Ahn[1], Woong-Chul Kang[1], Tae Joo Jeon[2], Namsik Chung[1], Jong-Doo Lee[2], and Sang-Ho Cho[3]

[1]Cardiology Division, [2]Department of Nuclear Medicine, [3]Department of Pathology, Yonsei University College of Medicine, Seoul, Korea.

Heart Vessels (2007) 22:393–397
DOI 10.1007/s00380-007-0985-x

ORIGINAL ARTICLE

Norihiko Senju · Satoshi Ikeda · Seiji Koga
Yoshiyuki Miyahara · Kunihiro Tsukasaki
Masao Tomonaga · Shigeru Kohno

The echocardiographic Tei-index reflects early myocardial damage induced by anthracyclines in patients with hematological malignancies

Questions not answered for anthracycline induced cardiotoxicity

- What is the predictive value of cardiac function monitoring during anthracycline therapy ?
- When should baseline cardiac function be monitored ?
- Should all patients receiving anthracyclines follow the same monitoring schedule?

- **Baseline cardiac function tests are generally accepted during anthracycline chemotherapy**
  - **Before or after a cummulative dose of 150 mg/m^2**
- **Some patients do not require baseline cardiac monitoring**

Questions not answered for anthracycline induced cardiotoxicity

- What is the predictive value of cardiac function monitoring during anthracycline therapy ?
- When should baseline cardiac function be monitored ?
- Should all patients receiving anthracyclines follow the same monitoring schedule?

- **Some patients with lower risk for anthracycline-induced cardiomyopathy**
  ➔ require less cardiac evluation

Consider *risk factors*
for anthracycline-induced cardiomyopathy

Doxorubicin-induced Cardiotoxicity

- **Prevention**
  - Maximal lifetime doxorubicin dose limitation (< 550 mg/m^2) → Safe doxorubicin dose ?
  - Changing the method of administration (bolus → continuous)
  - Use of cardioprotectant (dexrazoxane, amifostine, probucol,…)
  - Development of anthracycline lipid formulation and analogues (daunorubicin 900 mg/m^2, epirubicin 935 mg/m^2, idarubicin 225 mg/m^2)

Herceptin (Trastuzumab)-induced Cardiotoxicity

The New England Journal of Medicine

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VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

ABSTRACT

Background The *HER2* gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.

Methods We evaluated the efficacy and safety of trastuzumab, a recombinant monoclonal antibody against HER2, in women with metastatic breast cancer that overexpressed HER2. We randomly assigned 234 patients to receive standard chemotherapy alone and 235 patients to receive standard chemotherapy plus trastuzumab. Patients who had not previously received adjuvant (postoperative) therapy with an anthracycline were treated with doxorubicin (or epirubicin in the case of 36 women) and cyclophosphamide with (143 women) or without trastuzumab (138 women). Patients who had previously received adjuvant anthracycline were treated with paclitaxel alone (96 women) or paclitaxel with trastuzumab (92 women).

Results The addition of trastuzumab to chemotherapy was associated with a longer time to disease progression (median, 7.4 vs. 4.6 months; P<0.001), a higher rate of objective response (50 percent vs. 32 percent, P<0.001), a longer duration of response (median, 9.1 vs. 6.1 months; P<0.001), a lower rate of death at 1 year (22 percent vs. 33 percent, P=0.008), longer survival (median survival, 25.1 vs. 20.3 months; P=0.046), and a 20 percent reduction in the risk of death. The most important adverse event was cardiac dysfunction, which occurred in 27 percent of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management.

Conclusions Trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2. (N Engl J Med 2001; 344:783-92.)

DESPITE advances in the diagnosis and treatment of breast cancer, more than 44,000 women in the United States will die this year of metastatic disease.[1,2] Although objective responses to some chemotherapy regimens are common, few patients with metastatic disease are cured,[3,4] and treatments frequently cause substantial adverse effects.

A growth factor receptor gene,[5-7] human epidermal growth factor receptor (*HER2*), is amplified in 25 to 30 percent of breast cancers and in these cases the encoded protein is present in abnormally high levels in the malignant cells.[8,9] Women with breast cancers that overexpress HER2 have an aggressive form of the disease with significantly shortened disease-free survival and overall survival.[8-12] Laboratory studies indicate that amplification of *HER2* has a direct role in the pathogenesis of these cancers,[13-17] thereby providing investigators with an opportunity to target a therapeutic agent directly against the alteration.

Several murine monoclonal antibodies against the extracellular domain of the HER2 protein were found to inhibit the proliferation of human cancer cells that overexpressed HER2, both in vitro and in vivo.[18-20] To minimize immunogenicity, the antigen-binding region of one of the more effective antibodies was

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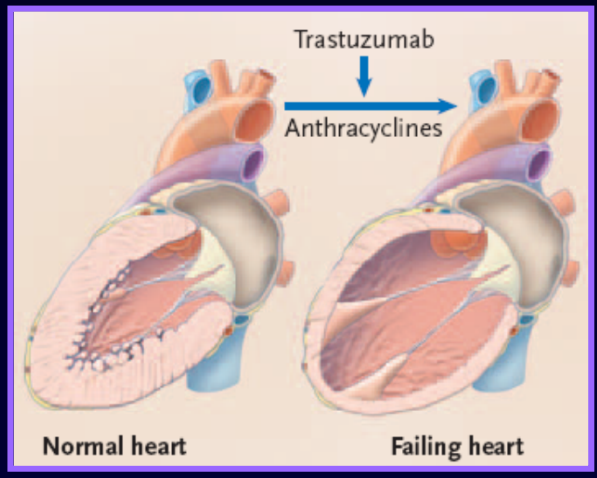
*Additional study investigators are listed in the Appendix.



- 27 % in herceptin & anthracyclines
- 13 % in herceptin & paclitaxel
- 5 % in herceptin only

Trastuzumab-induced Cardiotoxicity

Proposed mechanisms

- drug-drug interactions : enhance anthracycline cardiotoxicity
- block myocardial survival pathways response to stress

- **Risk factors**
  - old age
  - concurrent or prior anthracycline CTx
  - previous cardiac diseases
  - baseline decreased cardiac function….

Hudis CA, NEJM, 2007

Trastuzumab-induced Cardiotoxicity

First author	Reference	Year	Trastuzumab		Non-trastuzumab	
			Total number of patients	Cardiotoxicity (%)	Total number of patients	Cardiotoxicity (%)
Slamon	3	2001	235	22	234	4
Untch	14	2004	26	12	23	0
Piccart-Gebhart	9	2005	1677	9	1710	2
Tan-Chiu	7	2005	850	4	814	1
Jonesuu	35	2006	115	3	116	6
Papaldo	12	2006	35	20	33	6
Burstein	18	2003	54	4	–	–
Burstein	17	2003	40	12	–	–
Lunardi	21	2003	8	50	–	–
Gori	16	2004	25	8	–	–
Tripathy	13	2004	93	2	–	–
Ardavanis	19	2005	31	3	–	–
Bengala	20	2006	28	18	–	–
Chia	10	2006	30	23	–	–
Perik	11	2006	17	18	–	–

10 %

2 %

Panjrath, et al, Nuclear Med Comm, 2007

Trastuzumab-induced Cardiotoxicity

- **Unlike anthracyclines,**
  - does not dose-related
  - no apparent pathological abnormality on EM
  - less severe
  - seems more reversible

Needs long-term monitoring !

CTx-associated with Ischemia

Chemotherapy Agents	Incidence (%)	Frequency of Use
Antimetabolites		
Capecitabine (Xeloda) (71,74,83–85)	3–9	+++
Fluorouracil (Adrucil) (8,70,71,73–79)	1–68*	+++
Antimicrotubule agents		
Paclitaxel (Taxol) (90,91)	<1–5	+++
Docetaxel (Taxotere) (10,92)	1.7	++
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (10,93,94)	0.6–1.5	++
Small molecule tyrosine kinase inhibitors		
Erlotinib (Tarceva) (10)	2.3	+++
Sorafenib (Nexavar) (10,96)	2.7–3	+++

Yeh ETH, et al. JACC, 2009;53:2231-47

CTx-associated with HTN

Chemotherapy Agents	Incidence	Frequency of Use
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (Avastin) (18,19,107–112)	4–35	++
Small molecule tyrosine kinase inhibitors		
Sorafenib (Nexavar) (96,113–116)	17–43	+++
Sunitinib (Sutent) (37,118–122)	5–47	+++

- **Mechanism**
  - **VEGF inhibition ?**
  - **eNOS inhibition ?**

Yeh ETH, et al. JACC, 2009;53:2231-47

CTx-associated with HTN

- **Bevacizumab (Avastin)**
  - HTN in any time during CTx
  - Mostly adequately treated with anti-HTN medication
  - Worsening of HTN (1.7 %)
  - Hypertensive encephalopathy, CNS hemorrhage

- **Sorafenib (Nexavar)**
  - Most adverse side effect

Generally, need one more anti-HTN medication (prefer ACEi)
Sorafenib : consider drug-interaction
CYP3A4 pathway (prefer amlodipine, nefidipine)

Yeh ETH, et al. JACC, 2009;53:2231-47

CTx-associated with Venous Thromboembolism

Chemotherapy Agents	Incidence (%)	Frequency of Use
Alkylating agents		
Cisplatin (Platinol-AQ) (130)	8.5	+++
Angiogenesis inhibitors		
Lenalidomide (Revlimid) (144–149)	3–75*	+
Thalidomide (Thalomid) (133–143)	1–58*	+
Histone deacetylase inhibitor		
Vorinostat (Zolinza) (10,131,132)	4.7–8	+
Small molecule tyrosine kinase inhibitors		
Erlotinib (Tarceva) (10)	3.9–11	+++

Yeh ETH, et al. JACC, 2009;53:2231-47

CTx-associated with Venous Thromboembolism

- **Hypercoagulable state in cancer**

+

- **Chemotherapy**
  - ➢ **release of procoagulants and cytokines by tumor cell damage**
  - ➢ **direct endothelial damage**
  - ➢ **hepatotoxicity by CTx**

Yeh ETH, et al. JACC, 2009;53:2231-47

CTx-associated with Bradycardia

Chemotherapy Agents	Incidence (%)	Frequency of Use
Angiogenesis inhibitor		
Thalidomide (Thalomid) (138,140,156–159)	0.12–55*	+
Antimicrotubule agent		
Paclitaxel (Taxol) (10,90,91,154,155)	<0.1–31*	+++

- **Mechanism**
- **Effect on Purkinjie system or autonomic control ?**
- **Activation of histamine receptor ?**

Symptomatic vs. Asymptomatic

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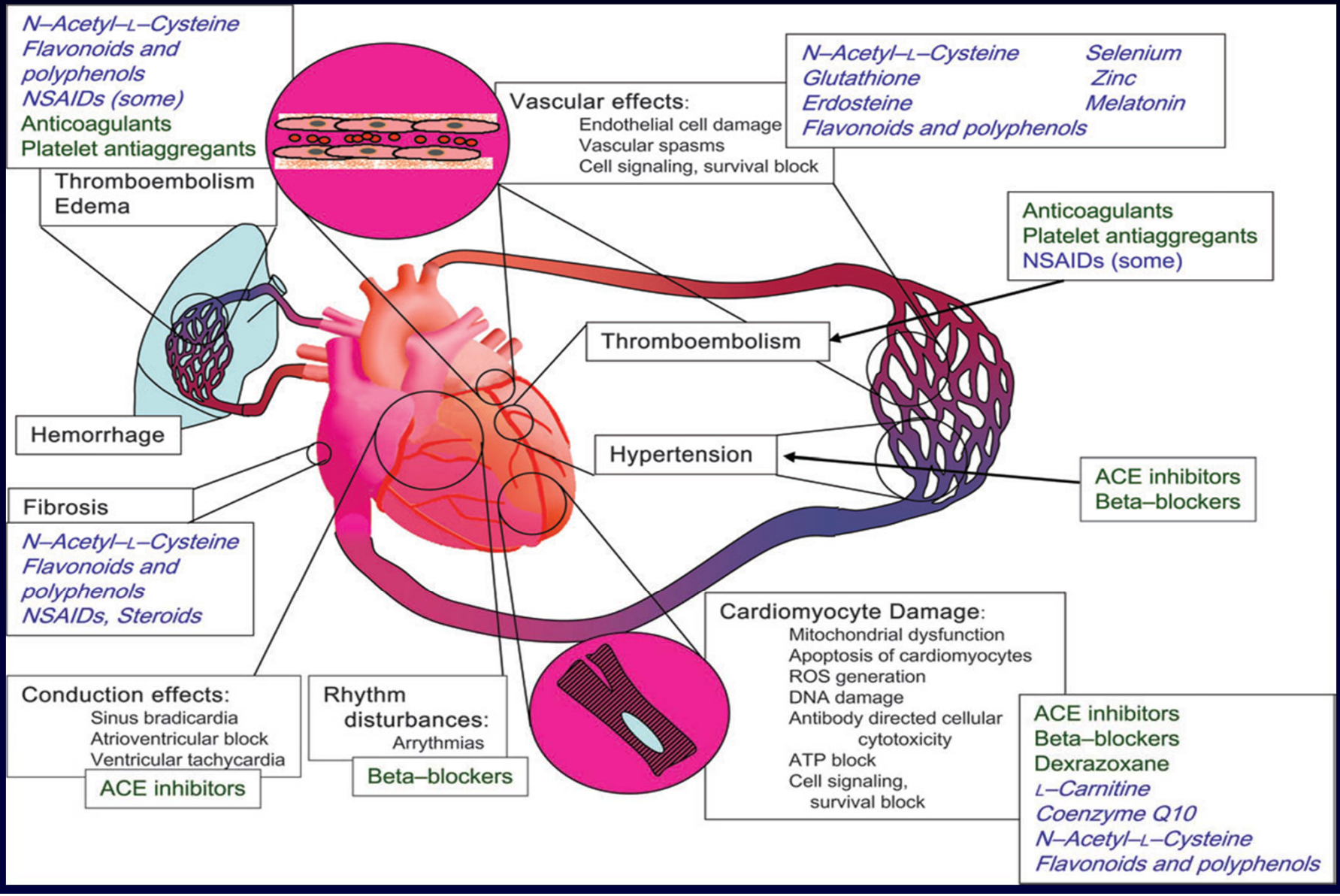
CTx-associated with QT prolongation

Table 6 Chemotherapy Associated With QT Prolongation*

Chemotherapy Agents	Incidence (%)	Frequency of Use
Histone deacetylase inhibitor		
Vorinostat (Zolinza) (10,131)	3.5–6	+
Miscellaneous		
Arsenic trioxide (Trisenox) (10,163–170)	26–93*	+
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	<1–3	++
Lapatinib (Tykerb) (10)	16	+
Nilotinib (Tasigna) (171–173)	1–10	+

- **Risk factors**
  - •Comorbid diseases (renal or hepatic dysfunction)
  - •Electrolyte imbalance (N/V, diarrhea..), female, bradycardia
  - •Concomitant medications (antiemetics, antifungals, quinolone antibiotics..)

Summary


N–Acetyl–L–Cysteine
Flavonoids and polyphenols
NSAIDs (some)
Anticoagulants
Platelet antiaggregants
Thromboembolism
Edema
Vascular effects:
Endothelial cell damage
Vascular spasms
Cell signaling, survival block
N–Acetyl–L–Cysteine
Glutathione
Erdosteine
Flavonoids and polyphenols
Selenium
Zinc
Melatonin
Anticoagulants
Platelet antiaggregants
NSAIDs (some)
Thromboembolism
Hypertension
ACE inhibitors
Beta–blockers
Hemorrhage
Fibrosis
N–Acetyl–L–Cysteine
Flavonoids and polyphenols
NSAIDs, Steroids
Cardiomyocyte Damage:
Mitochondrial dysfunction
Apoptosis of cardiomyocytes
ROS generation
DNA damage
Antibody directed cellular cytotoxicity
ATP block
Cell signaling, survival block
Conduction effects:
Sinus bradicardia
Atrioventricular block
Ventricular tachycardia
ACE inhibitors
Rhythm disturbances:
Arrythmias
Beta–blockers
ACE inhibitors
Beta–blockers
Dexrazoxane
L–Carnitine
Coenzyme Q10
N–Acetyl–L–Cysteine
Flavonoids and polyphenols

Conclusions

- Insufficient data
- Conflicting data
- Incomplete available guideline
- Lack of standard definition of cardiotoxicity

However, individualized baseline cardiac evaluation and monitoring are reasonable approach to chemotherapeutic agents -induced cardiotoxicity

Cardiologist **Hemato-oncologist**

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