CARDIOVASCULAR EFFECTS OF ANTHRACYCLINE-LIKE CHEMOTHERAPY AGENTS

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ANTHRACYCLINE AGENTS

- 1) DOXORUBICIN-Adriamycin
- 2) Daunorubicin-Cerubidine
- 3) Idarubicin-Idamycin
- 4) Epirubicin-Ellence

2 MAIN CATAGORYS

- ACUTE/SUBACUTE

-CAN ARRISE AT ANY TIME FROM INITIATION OF THERAPY TO WEEKS AFTER TREATMENT TERMINATION

- LATE/CHRONIC

TYPICALLY MANIFESTED AS CLINICAL HEART FAILURE OR SUBCLINICAL DECLINE IN MYOCARADIAL FUNCTION.

USUALLY OCCURS WITHIN ONE YEAR OFTER TREATMENT TERMINATION OR EVEN LATER, AFTER ONE YEAR OF TREATMENT END

ACUTE/SUBACUTE TOXICITY

- ECG ABNORMALITIES
- ARRHYMIAS(SVT/VT)
- HEART BLOCK
- LV DYSFUNCTION
- INCREASE BNP
- PERICARDITIS-MYOCARDITIS SYNDROME

ACUTE TOXICITY

- RELATIVELY UNCOMMON
- DOXORUBICIN 3.2%
- MOST ARE NOT LIFE-THREATENING
- RESOLVE WITHIN 1 WEEK
- MONITORING IS NOT RECOMMENDED OR REQUIRED IF NORMAL LV FUNCTION BY HISTORY, PHYSICAL EXAM OR TESTING

SUBACUTE TOXICITY

- MORE COMMON
- CHOP IS HIGHER RISK
- VARIES BETWEEN 11-21%

- Relationship between acute and developing subacute toxicity is not clear.

CHRONIC CARDIOTOXICITY

- CARDIOMYOPAHTY IS DOSE-LIMITING SIDE EFFECT OF ANTHRACYCLINES.
- USE OF ANTHRACYCLINES WAS ASSOCIATED WITH SIGNIFICANTLY INCREASED RISK OF BOTH CLINICAL AND SUBCLINICAL CARDIOTOXICITY.
- CARDIAC RELATED DEATHS(RARE) WAS ALSO SIGNIFICANTLY HIGHER

CLINICAL MANIFESTATIONS

- CHRONIC ANTHRACYCLINE RELATED CARDIOTOXICITY TYPICALLY PRESNETS EARLY, WITHIN 1 YR OFTER TERMINATION OF CHEMO.
- PEAK TIMING OF SYMPTOMS OF CHF IS ABOUT 3 MONTHS AFTER LAST ANTHRACYCLINE DOSE.
- MORTALITY IS HIGH(60%) BUT DECREASING DUE TO NEWER TREATMENTS.

CLINICAL MANIFISTATIONS

- HEART FAILURE CAN OCCUR MORE THAN A DECADE AFTER LAST DOSE.
- GREATEST CONCERN WHERE ANTHRACYCLINES ARE USED FOR CURATIVE OR ADJUVANT REGIMEN
- IN CHILDREN, LATE TOXICITY IS LV DYSFUNCTION, CARDIOMYOPATHY(57%)

CLINICAL MANIFISTATIONS

- LATE HEART FAILURE IS INCREASED IN ELDERLY WOMEN TREATED WITH ADJUVANT CHEMO CONTAINING ANTHRACYCLINES COMPARED TO NOT TREATED WITH THEM
- REGARDLESS OF TIMING, CHRONIC CARDIOMYOPATHY BEGINS WITH ASYMPTOMATIC DIASTOLIC OR SYSTOLIC DYSFUNCTION, PROGRESSING THE CHF

CLINICAL MANIFISTATIONS

- ALTHOUGH TREATABLE, CUMULATIVE CARDIOTOXICITY IS A RESULT OF PERMANENT LOSS OF CARADIOMYOCYTES AND GENERALLY NOT REVERSIBLE

MECHANISMS

- ALTHOUGH ANTHRACYCLINE RELATED CARDIOTOXICITY IS WELL KNOWN THE MECHANISM IS NOT
- OVEREXPRESSION OF FREE RADICAL SCAVENGERS
- INHIBITION OF FORMATION OF PEROXYNITRATE

RISK FACTORS

- STRONGEST PREDICTOR IS CUMULATIVE DOSE

- HOWEVER, AGE AT TIME OF DRUG EXPOSURE, CONCOMITANT ADMINISTRATION OF OTHER CARDIOTOXIC AGENTS(PACLITAXEL AND TRASTUZUMAB) OR CHEST RADIATION OR PREEXISTING CV DISEASE ALSO INCREASE RISK

- LONG TERM SURVIVAL IS A RISK!-PROVEN THAT DETERIORATION OF CARDIAC FUNCTION OCCURS UP TO 30 YEARS

CUMULATIVE DOSE

- IN ONE STUDY 88% OF PTS TREATED WITH ANTHRACYCLINES DEVELOPED SYMPTOMATIC HEART FAILURE
- 0.14% RECEIVED< 400 MG/M2
- 7% RECEIVED 550 MG/M2
- 18% BEYOND 700 MG/M2
- DOXORUBICIN RELATED CARDIOTOXICITY IS UNDERESTIMATED. 26% PTS RECEIVING 550MG/M2 DEVELOPED CHF

CUMULATIVE DOSING

- THEREFORE IT IS GENERALLY ACCEPTED CUMULATIVE DOXORUBICIN DOSES BE LIMITED TO 450-500 MG/M2

ALTHOUGH LIMITING THE LIFETIME CUMULATIVE DOSE OF ANTHRACYCLINES IS IMPORTANT TO PREVENTION, SURVEILLANCE OF MYOCARDIAL FUNCTION DURING AND AFTER THERAPY, WITH EARLY DETECTION OF ADVERSE CARDIAC EFFECTS REMAINS THE PRINCIPAL METHOD OF PREVENTING ANTHRACYCLINE CARDIOTOXICITY.

PRE-TREATMENT

- Beta-blockers- carvedilol may be benefit. 50 pts. treated with anthracycline. Half got carvedilol. Echo after 6 months showed no change in LVEF after chemo. Pts. assigned to placebo had 17% reduction in EF.
- High risk pts. needing anthracycline chemo may be considered for beta blocker therapy.

ACE INHIBITORS

ACE inhibitors and angiotensin II receptor blockers (ARBs) have been shown to improve outcomes and slow disease progression in patients with left ventricular systolic dysfunction due to a variety of causes.

NONINVASIVE MONITORING OF LVEF

- NO GUIDELINES FOR PRE ASSESSMENT OR EVALUATION PRIOR TO CHEMO TREATMENT
- RISK ASSESS-IF HIGH, CONSIDER LV EVALUATION OR CARDIOLOGY CONSULT
- MONITORING OF CARDIAC FUNCTION IS HIGHLY RECOMMENDED BEFORE, DURING AND AFTER ALTHOUGH NO CLEAR GUIDELINES ON FREQUENCY OR OPTIMAL METHOD OF LVEF ASSESSMENT ARE GIVEN

LVEF ASSESSMENT

- ECHO-METHOD OF CHOICE
- EASY
- NO RADIATION
- REPRODUCABLE
- RNA-EARLY GOLD STANDARD BUT NOW HAS BEEN REPLACED WITH ECHO

CARDIAC MRI

- SELECT PTS
- USED WHEN ECHO HAS POOR WINDOWS

ECHOCARDIOGRAPHY

- ANY CLINICAL SUSPISION OF CHANGE
- REALLY ONLY EFFECTIVE IN ACUTE TOXICITY
- DOESN'T HELP WIT LATENT PERIOD CHANGE
- STRESS AND STRAIN RATES MAY BE FUTURE

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  - NO CONSENSUS FOR MONITORING BUT DIASTOLIC FUNCTION, STRAIN AND TISSUE DOPPLER SHOW PROMISSING FUTURE