Anthracycline-induced cardiotoxicity: Prevention by dexrazoxane (Cardioxane) and Pegylated Liposomal Doxorubicin (DOXIL) Relevance to breast cancer treatment

Alberto Gabizon,
Shaare Zedek MC

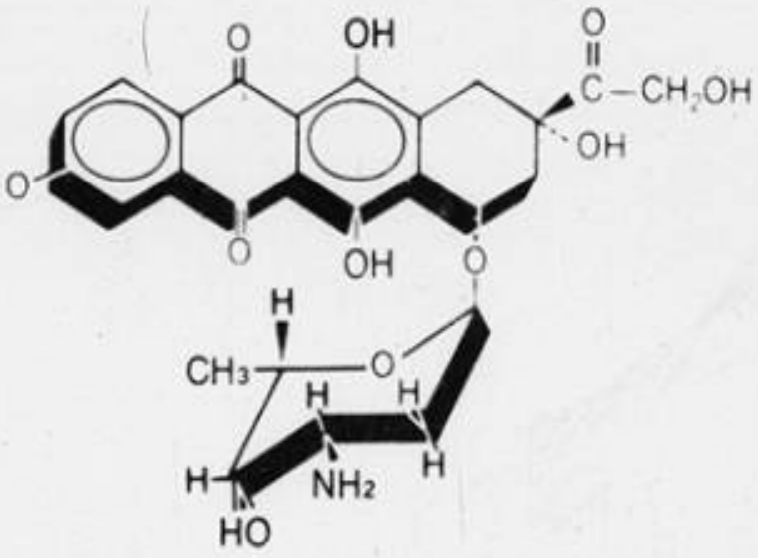
Thanks to Megapharm for providing part of the supporitng slide material

Anthracyclines: A Cornerstone of Cancer Therapy

- Potent cytotoxic agents that have been the mainstay of chemotherapy for over 30 years
- Amongst the most widely used treatments for cancer
- Several analogues available:
  - doxorubicin
  - daunorubicin
  - epirubicin
  - Idarubicin
- Related compound: Mitoxantrone
- Special formulations: Pegylated liposomal doxorubicin (DOXIL, Caelyx), Non-pegylated liposomal doxorubicin (Myocet), Liposomal daunorubicin (Daunoxome)

Cellular effects of doxorubicin (adriamycin)

DNA



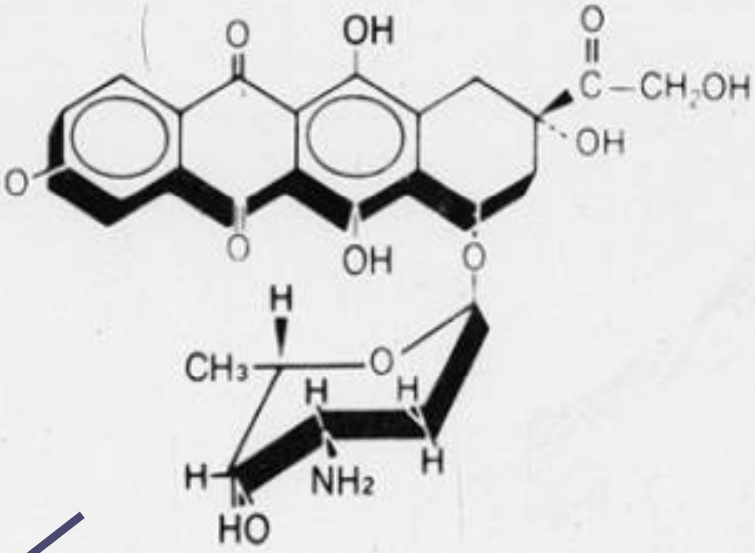
Intercalation

Adriamycin-DNA complex

Inhibition of DNA Topoisomerase II
Binding to mitochondrial cardiolipin
Uncoupling of oxidative phosphorylation
Production of Free Radicals (+Iron)

Adriamycin (Doxorubicin)

DNA



Adriamycin-DNA complex

Intercalation

Free Radicals /Mitochondrial damage

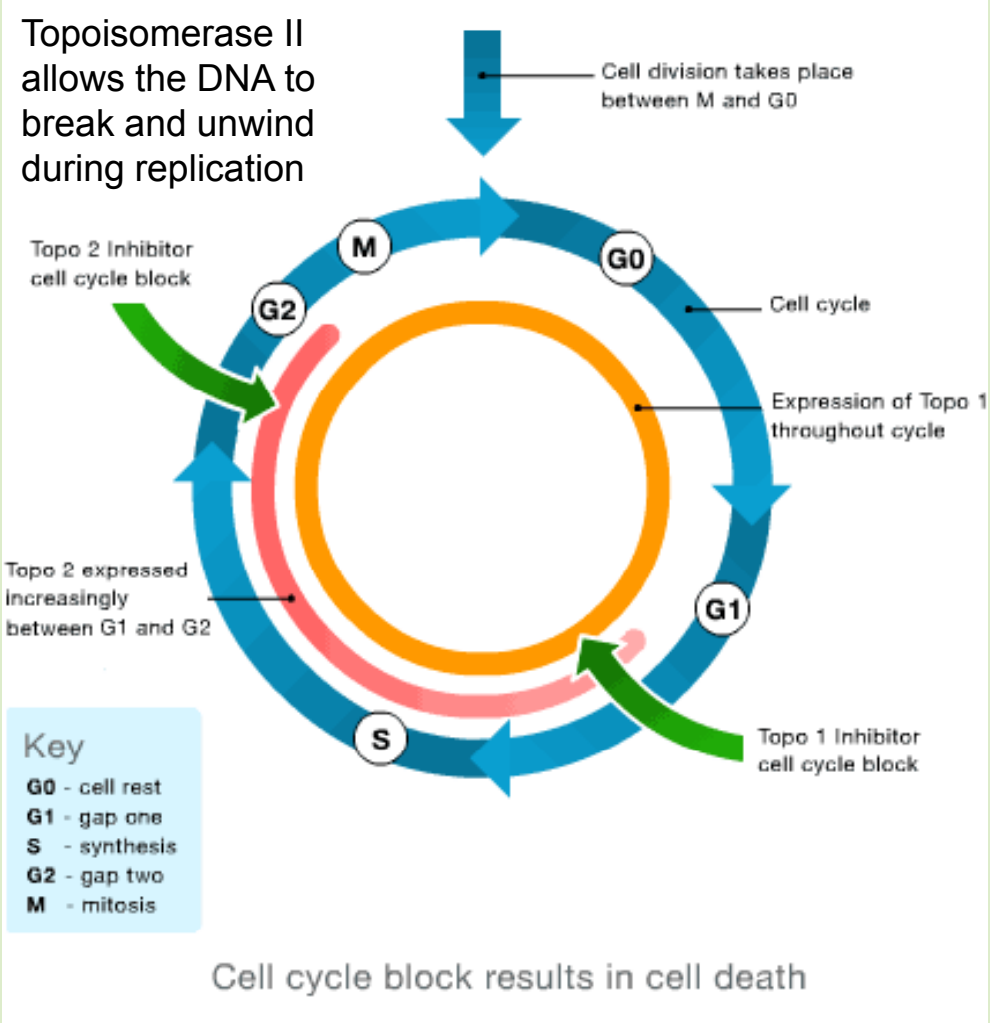
Cardiotoxicity

Inhibition of Topo II

Antitumour Effect

Anthracycline - Mechanism of Cell Damage

- **Topo II inhibition: Stabilization of the unwound DNA-Topo II complex and prevent sealing of double ended breaks**
- **Free radical damage (mitochondria, iron mediated)**
- **Membrane perturbation and apoptotic signalling**



Cardiac Toxicities of Anthracyclines

- **Acute**
  - Immediately after the infusion
  - Tachycardia, Arrhythmias,
  - Pericardial effusion, Pericarditis
- **Chronic**
  - Cumulative Dose related, Within 1 year of therapy
  - Heart failure, arrythmias
- **Late Onset** (usually triggered by 2nd insult)
  - Several years after stopping doxorubicin
  - Heart failure, arrhythmias

Anthracycline - Mechanism of Cardiotoxicity

- Myocardiocytes are extremely rich in mitochondria (50% weight)
- Anthracycline-induced cardiotoxicity results from free radical production (catalyzed by intracellular iron) and mitochondrial damage
- Affinity of anthracyclines to cardiolipin, a major component of mitochondria may play a role

Myocardial Injury Can Ultimately Result in Congestive Heart Failure (CHF)

Myocardial injury

Loss of cardiomyocytes

Left ventricular dysfunction

CHF

Methods Of F/U and Detection of Heart Damage

- **ECHO/MUGA:** **Most commonly used, not suitable for investigating early cardiac damage.**

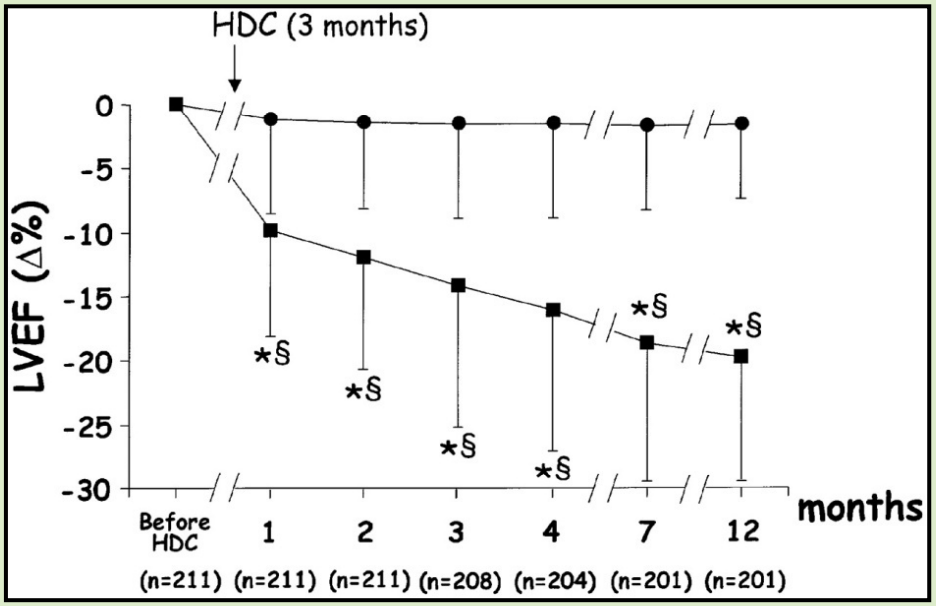
- **Endomyocardial Rt ventricular biopsy with EM examination (Billingham score): Accurate information on myocardial damage, remains research tool, requires special expertise**

- **Troponin T / I:**
  - **Elevation of serum cardiac Troponins shortly after anthracycline injection (hours, days)**
  - **May serve as an early parameter to identify patients at high risk**

Myocardial injury revealed by plasma Troponin Myocardial injury revealed by plasma Troponin I

D. Cardinale et al. Ann Oncol. 2002

- **211 women with breast cancer received epirubicin as adjuvant treatment.**



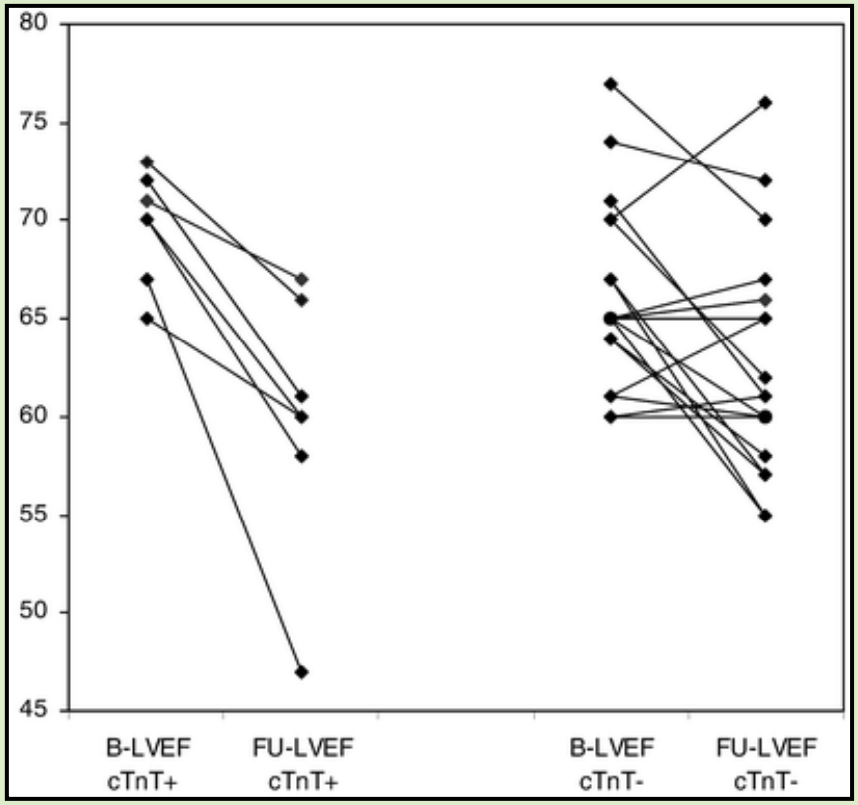
LVEF percentage changes during the follow-up in TnI + (■) and TnI - (●) patients* .P <0.001versus before HDC ;P < 0.01versus TnI –group

- **Patients with TnI$^+$ had a significant reduction in LVEF after one month; the TnI$^-$ patients didn't show any significant decrease in LVEF.**

Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies

H. W. Auner et al. Ann. Hematol. 2003

- **78 patients with hematological malignancies received anthracycline**



Left ventricular ejection fraction at baseline (*B-LVEF*) and follow-up (*FU-LVEF*) of patients with *cTnT+* and *cTnT-*

- **Patients with Tnt^{pos} had a significant reduction in LVEF; the Tnt^{neg} patients didn't show any significant decrease in LVEF.**

Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials

S.M. Swain et al. Cancer 2003

A Retrospective Analysis of 630 patients (two studies in patients with breast carcinoma and one study in patients with SCL carcinoma)

- **24% of patients who received doxorubicin developed <u>cardiotoxicity</u> (defined as LVEF 20% drop or 5%<LLN):**

16% → 150-250 mg/m^2 doxorubicin

18% → 350 mg/m^2 doxorubicin

38% → 450 mg/m^2 doxorubicin

65% → 550 mg/m^2 doxorubicin

Doxorubicin-related <u>CHF</u>:

5% → 400 mg/m^2 doxorubicin

16% → 500 mg/m^2 doxorubicin

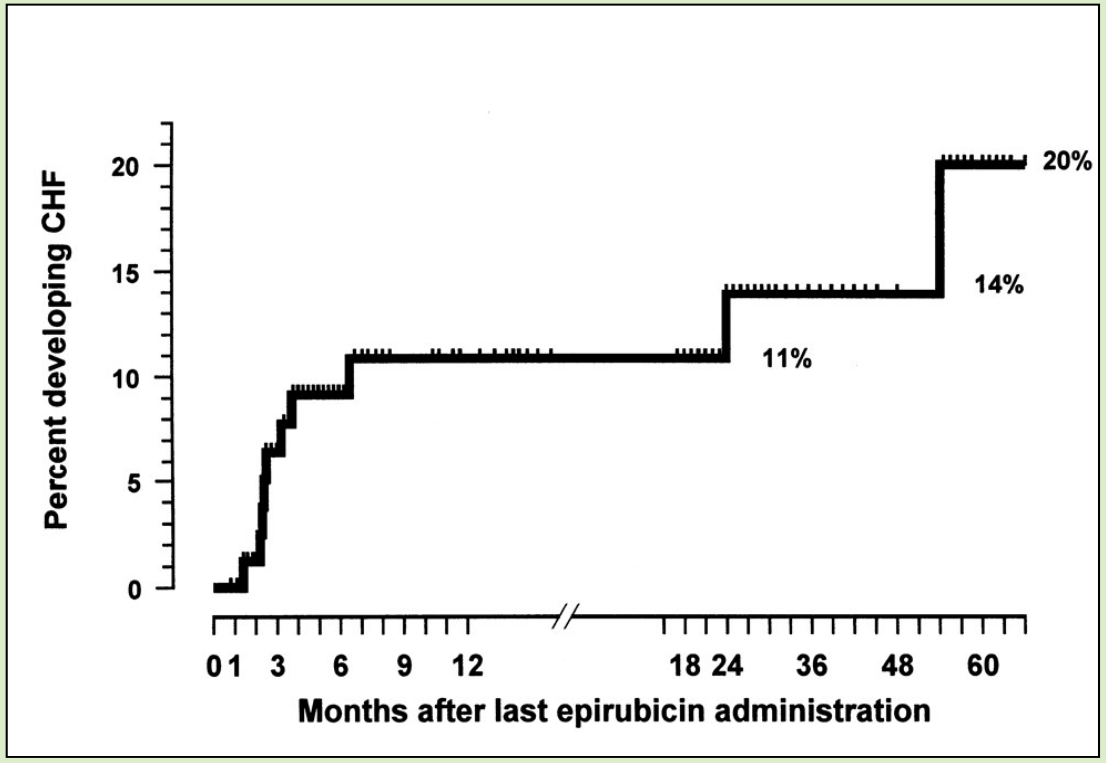
26% → 550 mg/m^2 doxorubicin

Actuarial risk of developing CHF after epirubicin (850–1000 mg/m^2): A prospective, blinded, long-term observational study of outcome in 120 patients

B. V. Jensen et al. Ann Oncol. 2002

- 20% of the patients developed CHF :
  - 11% ➔after 1 year
  - 14% ➔ after 2 years
  - 20% ➔ after 5 years

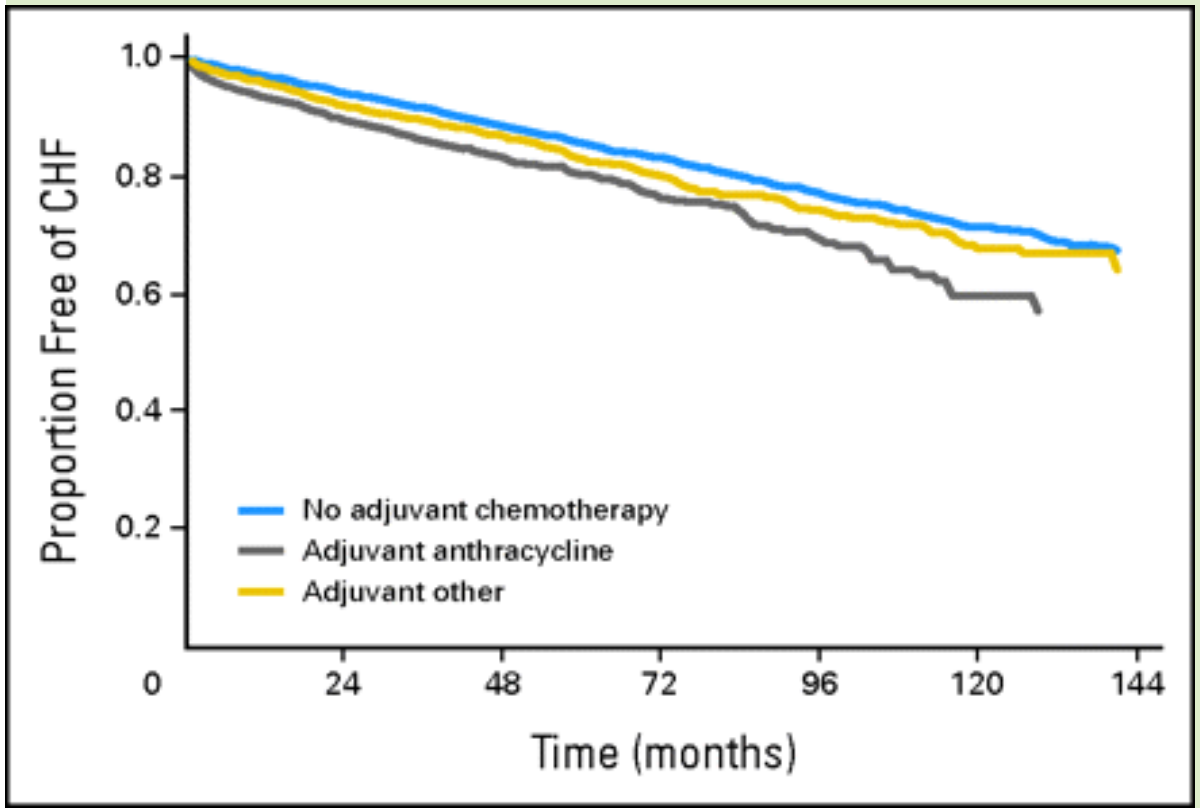
Bars indicate patients at risk at latest follow-up or death without CHF



Congestive Heart Failure (CHF) in Older Women over 65-yr old Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer

M.C. Pinder, Z. Duan et al. JCO 2007

- Date from Medicare database - 1992 to2002
- 43338 women with no history of CHF
- Diagnosed with stage I to III breast cancer



Women aged 66 to 70 years: freedom from congestive heart failure (CHF) by adjuvant chemotherapy type

Effect of Doxorubicin Plus Cyclophosphamide on Left Ventricular Ejection Fraction in Patients With Breast Cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial

Edith A. Perez et al. JCO 2004

Evaluation of changes in LVEF after four cycles of adjuvant AC in 1458 women with HER-2 positive breast cancer

- **Patients were treated with AC (60mg/m^2 doxorubicin plus 600mg/m^2 cyclophosphamide) for four cycles and then continued treatment per randomization to one of three arms. LVEF was monitored before and 3 weeks after AC by Echo or MUGA**
- **37 patients (2.5%) had an LVEF decrease >15%**
- **42 patients (2.9%) had ≤15% decrease in LVEF and LVEF that decreased to or below the LLN**

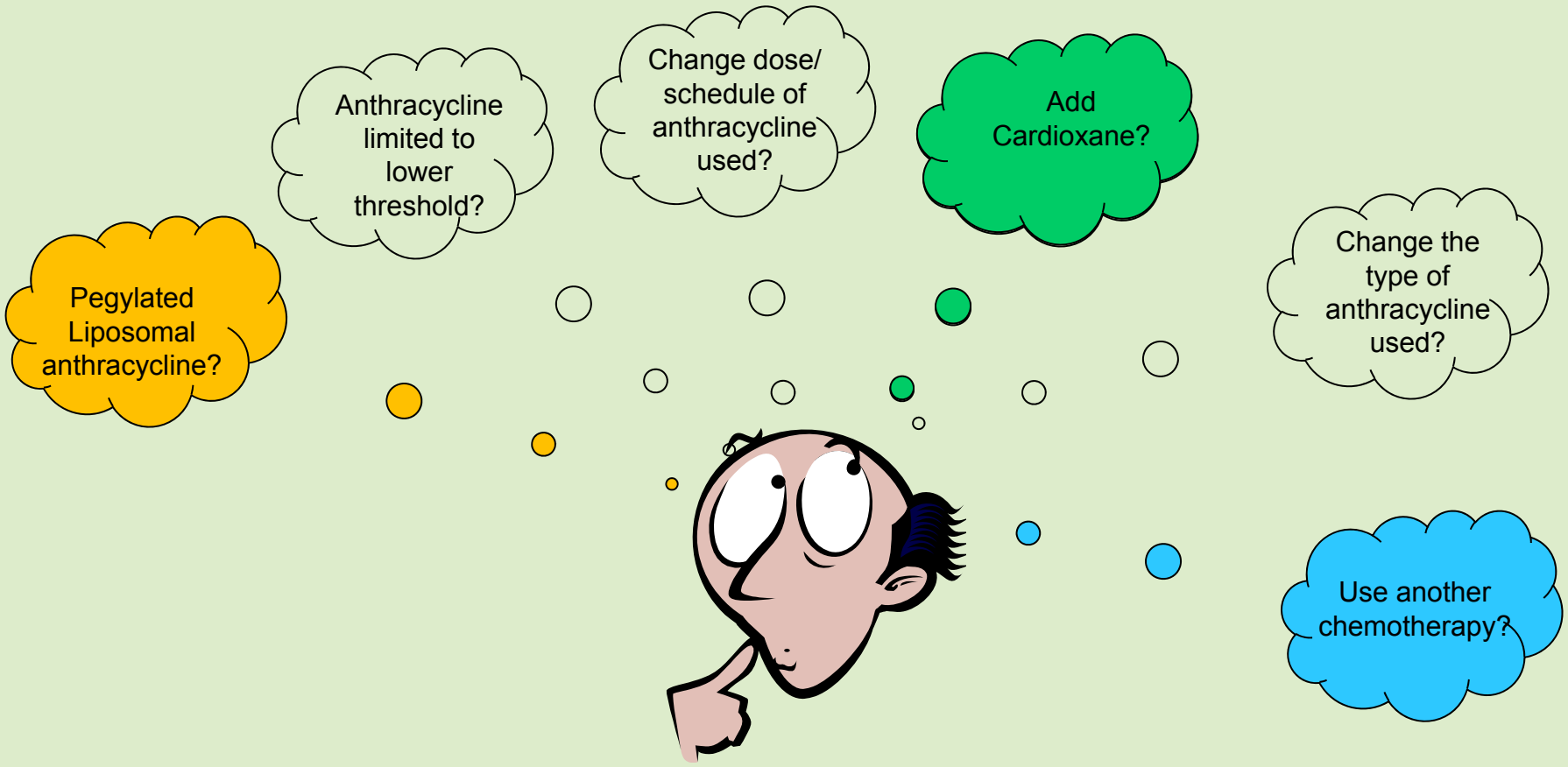
Summary

- Anthracycline cardiotoxicity
  - occurs from the very first dose
  - is irreversible
  - may lead to an insidious, progressive decline in cardiac function
  - may present many years after treatment

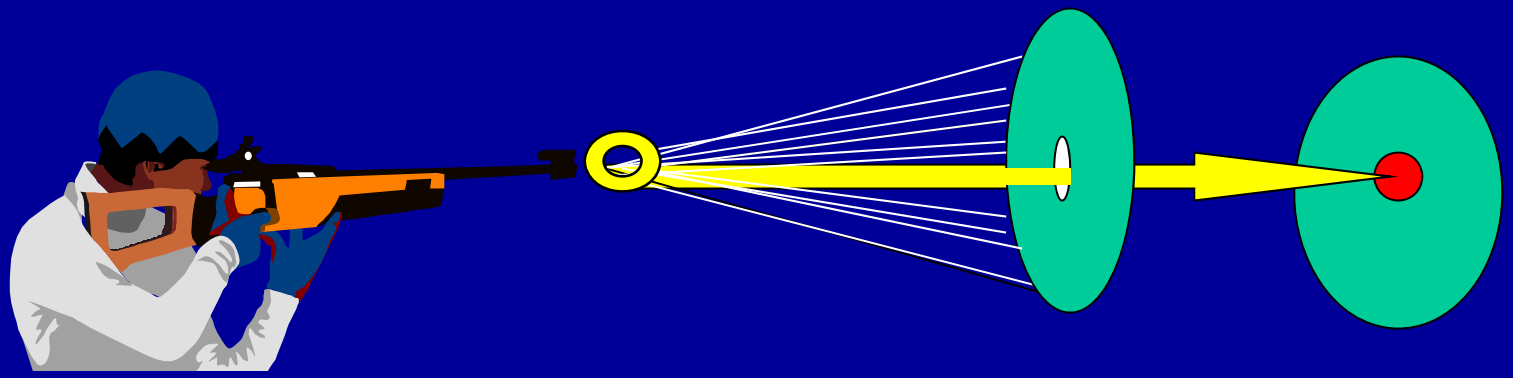
Five year update - Adjuvant Herceptin post-AC (ASCO 2007)

- 7.5% of patients did not meet criteria to begin Trastuzumab
- 16% could not receive full Herceptin plan due to LVEF drops
- Trastuzumab after anthracyclines has a CHF rate up to 3.9%
- Four statistically significant risk factors:
  - age $\geq$ 50 years
  - Hypertension medication
  - Baseline LVEF
  - Post-AC LVEF

Cardiotoxicity Prevention Strategies



Making Chemotherapy Cardiac Safe

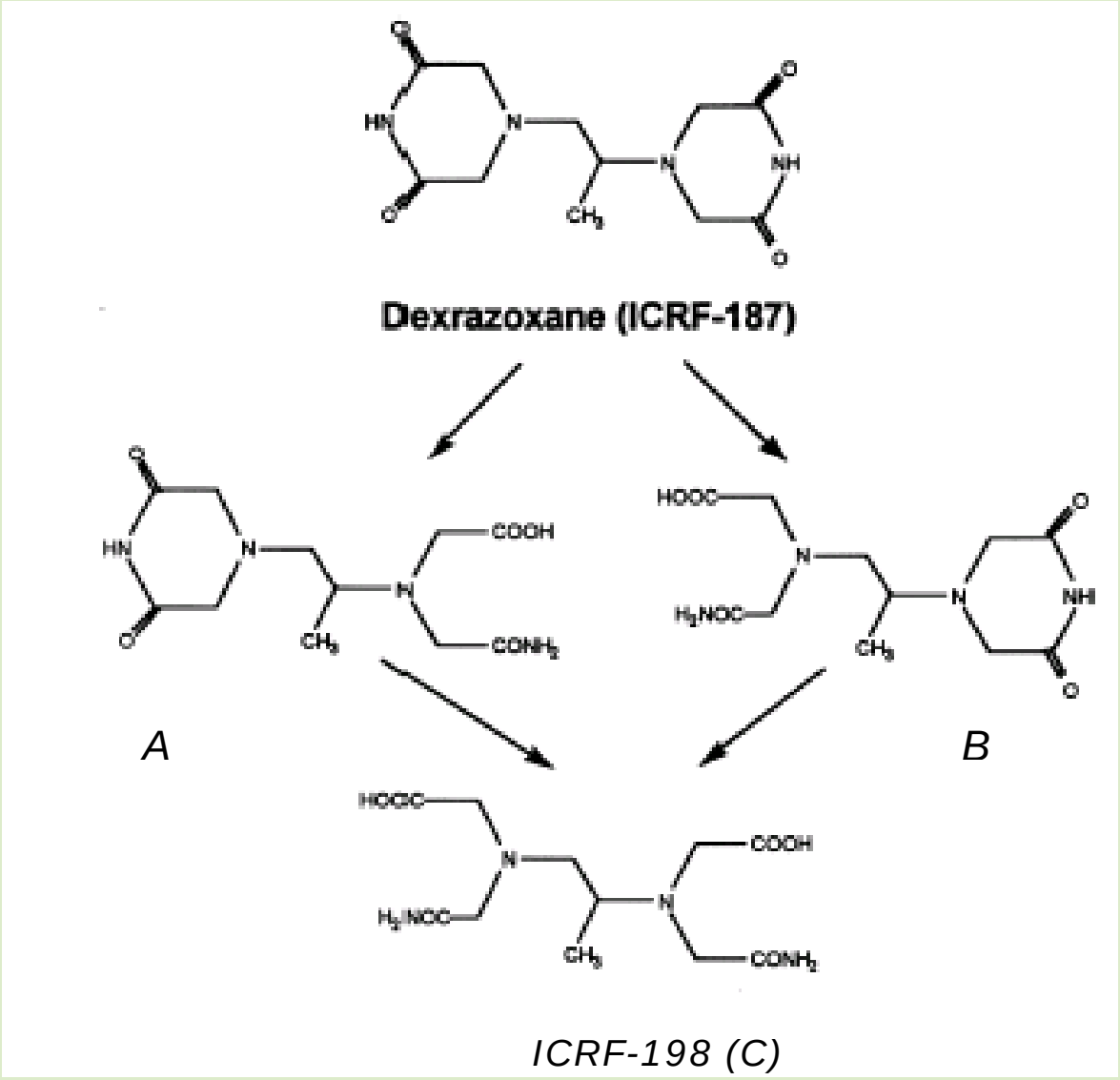


<u>Prevention of side effects</u>
Reduction of “Collateral Damage”
cytoprotective agents

<u>Heart Sparing with Targeted</u>
<u>Drug Delivery</u>

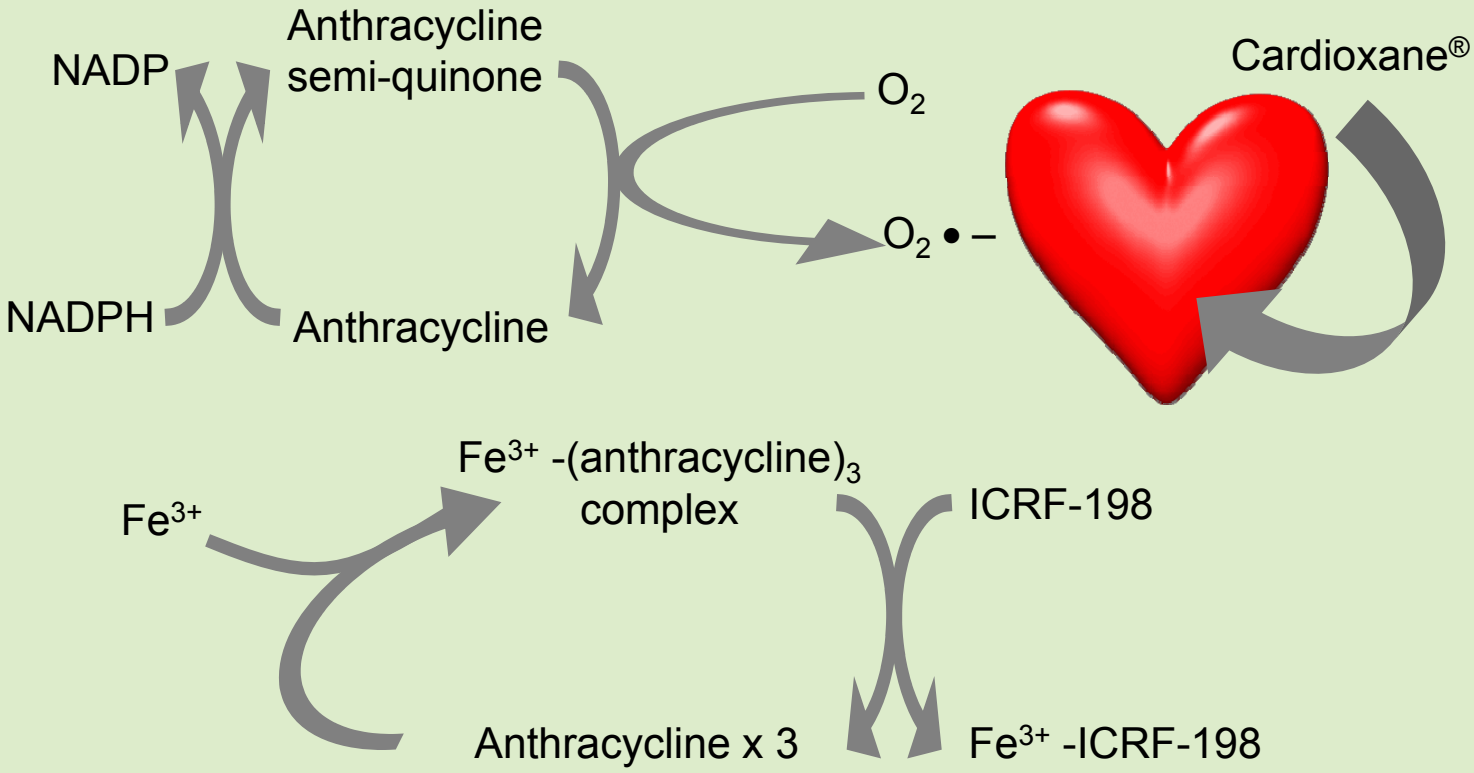
Cardioxane (dexrazoxane : ICRF – 187) structure and metabolites

More Cell Penetration



More Activity

Cardioxane – Mechanism of Cardioprotection



NADP = nicotinamide adenine dinucleotide phosphate; NADPH = reduced NADP

Dexrazoxane in the Lab

Preclinical studies indicate that the growth-inhibitory effects of doxorubicin and daunorubicin are NOT affected by pretreating tumor cells with dexrazoxane.

In contrast, under similar conditions, dexrazoxane strongly protects cardiac myocytes from doxorubicin-induced lactate dehydrogenase release.

(Wu and Hasinoff, ACD 2005)

Cardioxane (ICRF-187) permits longer treatment with doxorubicin in women with breast cancer

JL Speyer et al. JCO. 1992

- 150 patients with advanced breast cancer treated with FAC chemotherapy. Initial LVEF: ≥50%

- Open, randomized test comparing one group (n=76) receiving dexrazoxane and a control group (n=76)

Treatment Received

- Median cumulative dose of Dox: 500 mg/m^2 in the dexrazoxane group Vs 441 mg/m^2 in the control group.

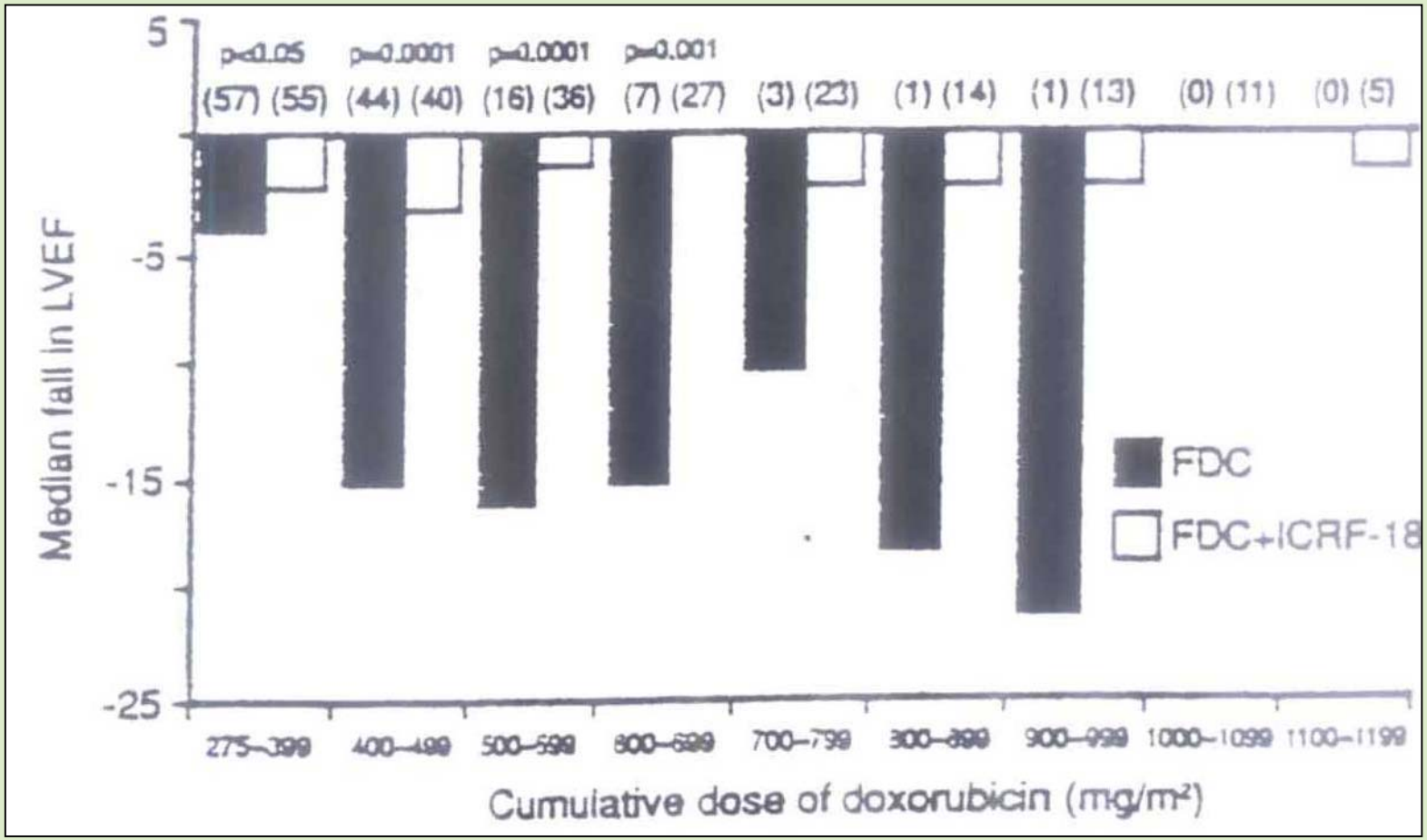
- Median number of cycles received:
  11 in the dexrazoxane group *vs* 9 in the control group.

- 26 patients in the dexrazoxane group could receive more then 700 mg/m^2 Dox *vs* 3 in the control group.

- 11 patients in the dexrazoxane group could receive more then 1000 mg/m^2 of doxo *vs* 0 in the control group.

ICRF-187 permits longer treatment with doxorubicin in women with breast cancer

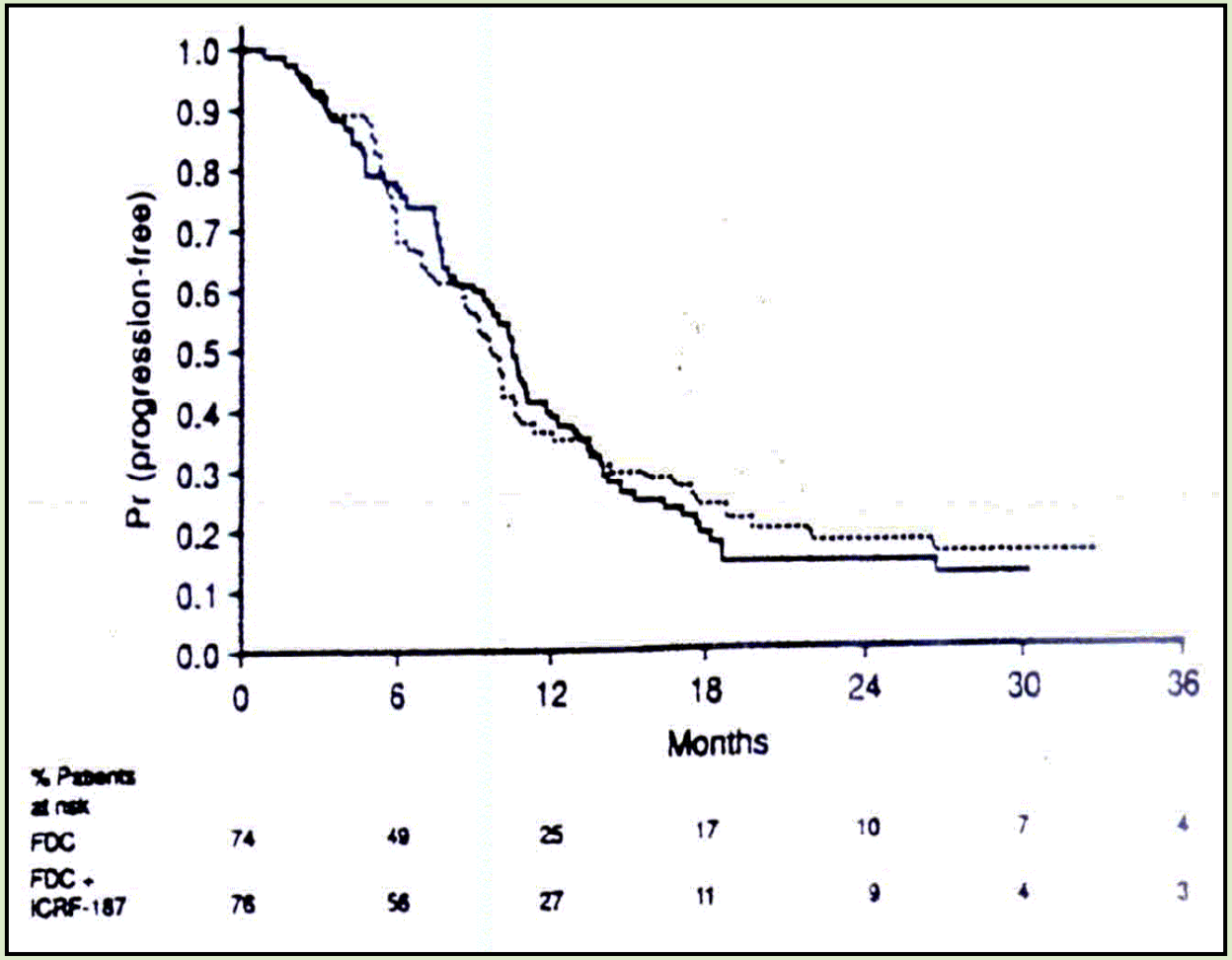
JL Speyer et al. JCO. 1992



Median fall in LVEF with increasing cumulative doses of doxorubicin

ICRF-187 permits longer treatment with doxorubicin in women with breast cancer

JL Speyer et al. JCO. 1992



FDC control arm (…….)

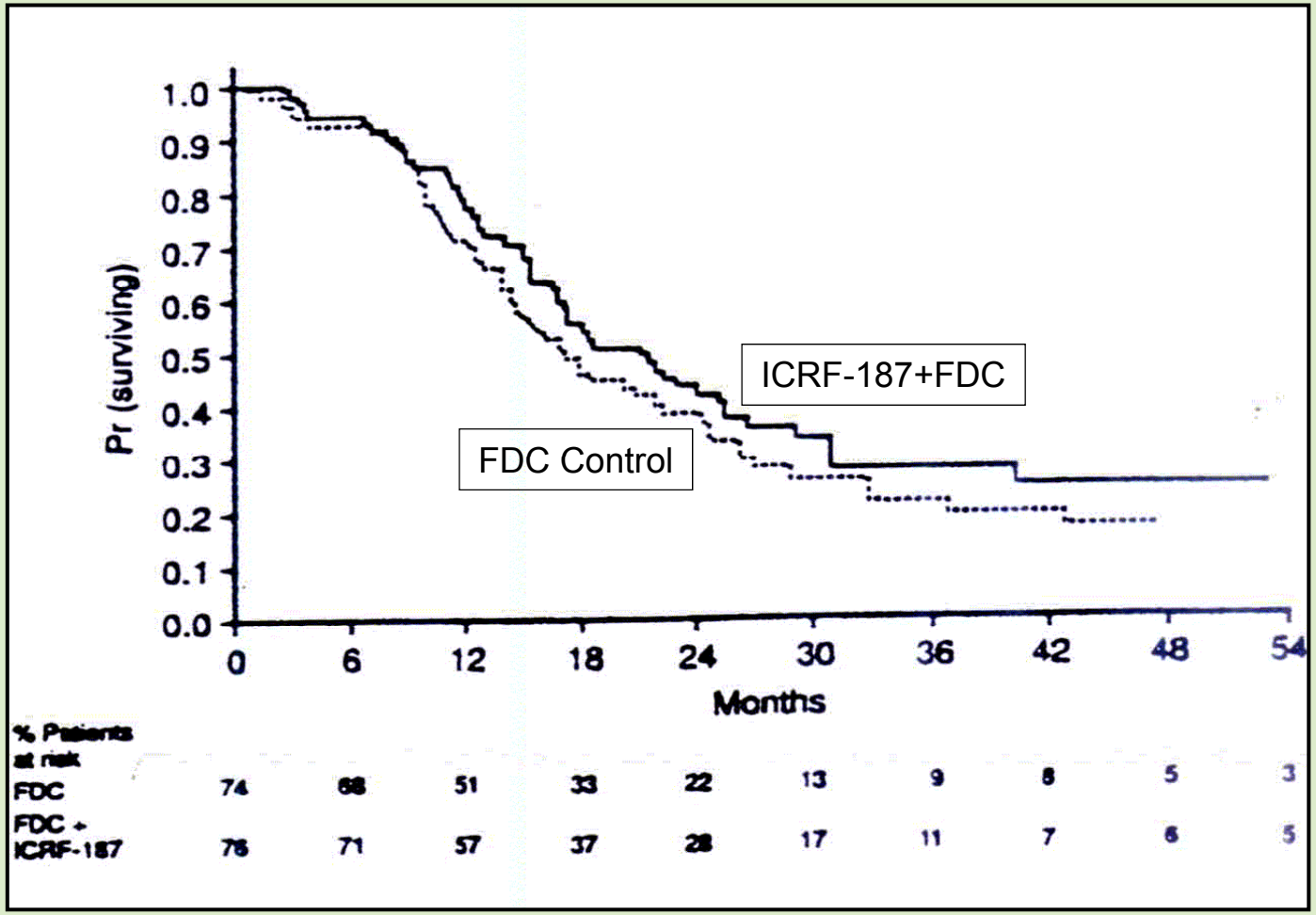
ICRF-187+FDC (---------)

Progression-free survival

No difference in relapse-free survival

ICRF-187 permits longer treatment with doxorubicin in women with breast cancer

JL Speyer et al. JCO. 1992



No difference in overall survival!

FDC=5FU, Doxo, Cyclophos

Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer

Swain SM et al. JCO. 1997

Two large multicenter controlled trials (088001 & 088006):

- **31% cardiac events in the placebo group *vs* 14% in the dexrazoxane group.**
- **8% of patients with CHF in the placebo group *vs* 0% in the dexrazoxane group.**
- **The overall risk of having a cardiac event was 2.5 greater for patients who did not receive dexrazoxane .**

Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer

Swain SM et al. JCO. 1997

Analysis of antitumoral responses

- **Time without progression:**
  No significant difference between the 2 groups

- **Median survival:**
  882 days in the DOX+DEX group *vs* 460 days in the DOX group

- **Number of cycles received:**
  36% of the patients in the DOX-DEX group received at least 15 cycles of chemotherapy *vs* 5% in the DOX group

Cardioprotective interventions for cancer patients receiving anthracyclines (Review)

van Dalen EC, Caron HN, Dickinson HO, Kremer LCM.

The Cochrane Library 2008, Issue 2

THE COCHRANE COLLABORATION®

Objectives

"The objective of this review was to assess the efficacy of different cardioprotective agents in preventing heart damage in cancer patients treated with anthracyclines"

Main results

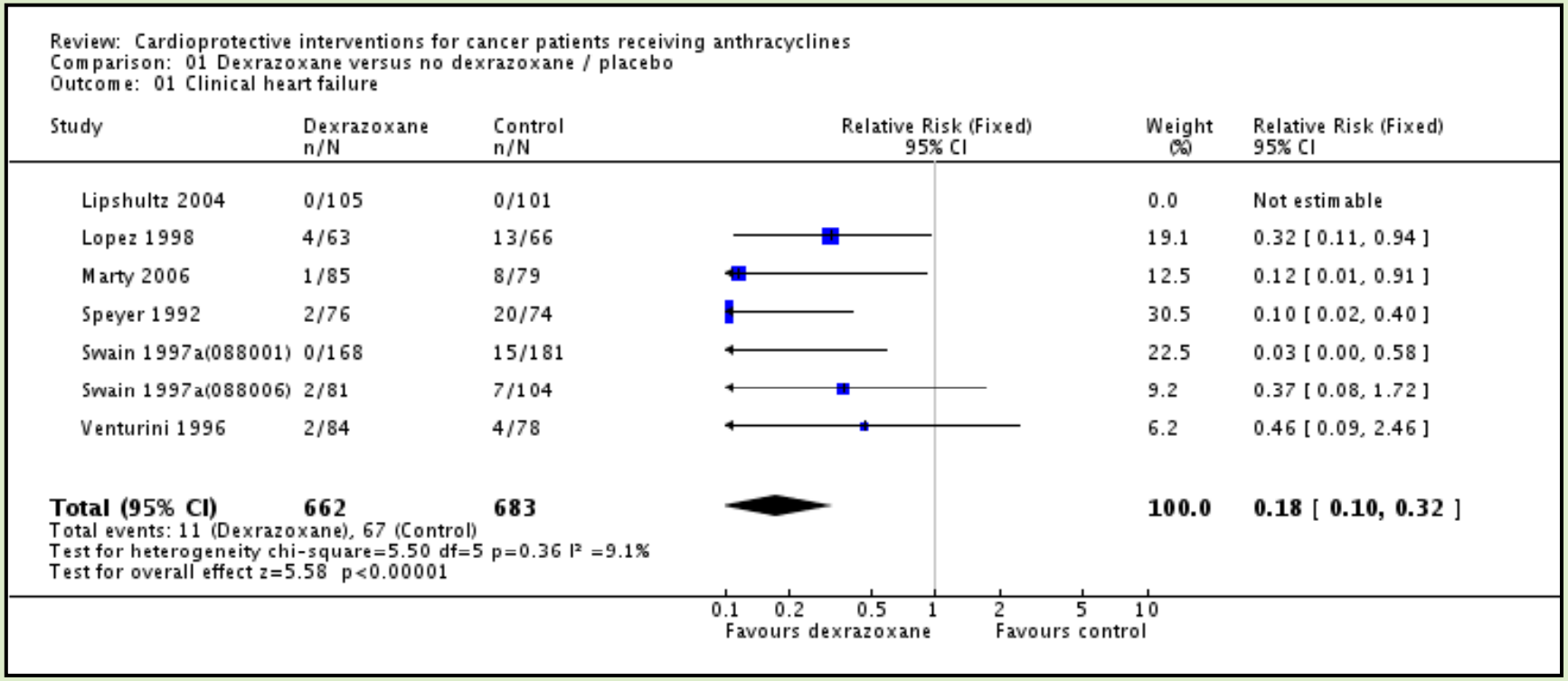
"… The nine included studies of dexrazoxane enrolled 1403 patients. The meta-analysis of dexrazoxane showed a statistically significant benefit in favour of dexrazoxane for the occurrence of heart failure (Relative Risk (RR) 0.29, 95% CI 0.20 to 0.41)."

Cardioprotective interventions for cancer patients receiving anthracyclines (Review)

van Dalen EC, Caron HN, Dickinson HO, Kremer LCM.
The Cochrane Library 2008, Issue 2

THE COCHRANE COLLABORATION®

- ***Clinical heart failure*** **- The meta-analysis showed a benefit in favour of dexrazoxane use (RR 0.18, 95% CI 0.10 to 0.32, P < 0.00001).**



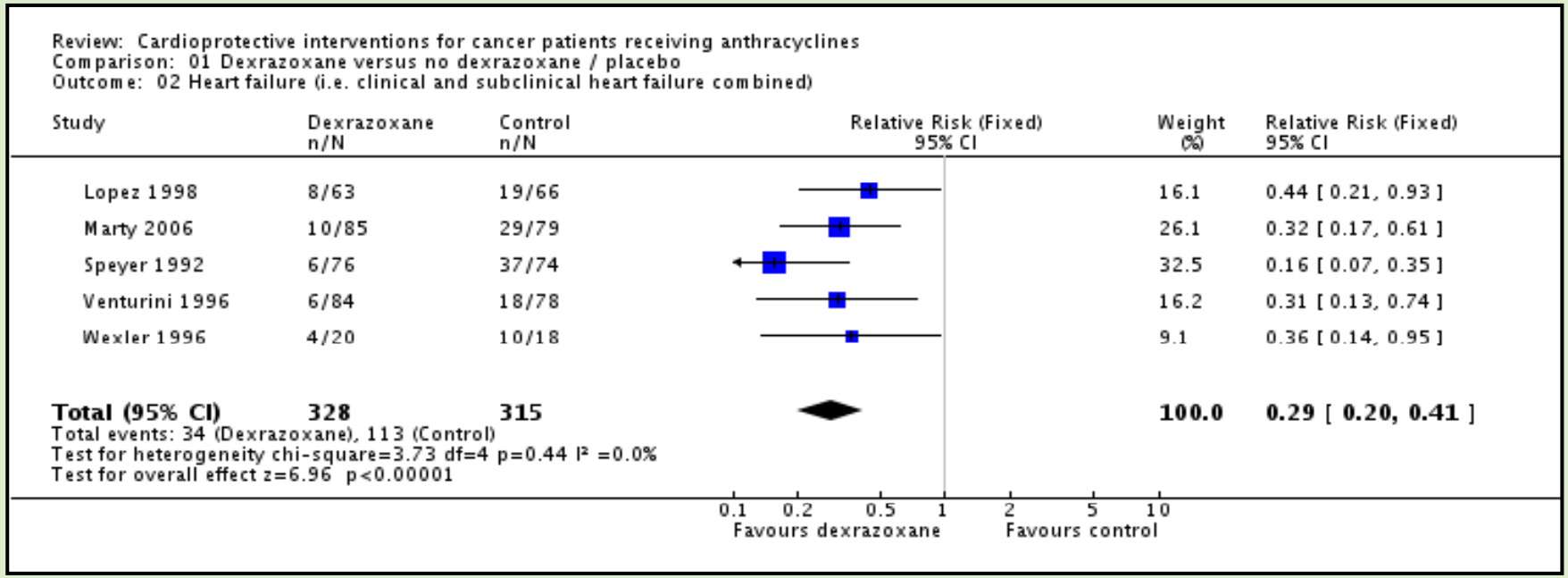
Cardioprotective interventions for cancer patients receiving anthracyclines (Review)

van Dalen EC, Caron HN, Dickinson HO, Kremer LCM.

The Cochrane Library 2008, Issue 2

THE COCHRANE COLLABORATION®

- ***Heart failure (i.e. clinical and subclinical heart failure combined)*** **- The meta-analysis showed a benefit in favour of dexrazoxane use (RR 0.29, 95% CI 0.20 to 0.41, P < 0.00001).**



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- ***adverse effects***-

  Among 19 possible side effects reviewed, only one showed a significant association with dexrazoxane:

  abnormal white blood cell count - the meta-analysis showed a significant difference in favour of the control treatment (RR 1.16, 95% CI 1.05 to 1.29, p = 0.005)

- **The clinical significance is unclear since neutropenia was not found to be worsened by dexrazoxane**

Cardioprotective interventions for cancer patients receiving anthracyclines (Review)

van Dalen EC, Caron HN, Dickinson HO, Kremer LCM.
The Cochrane Library 2008, Issue 2

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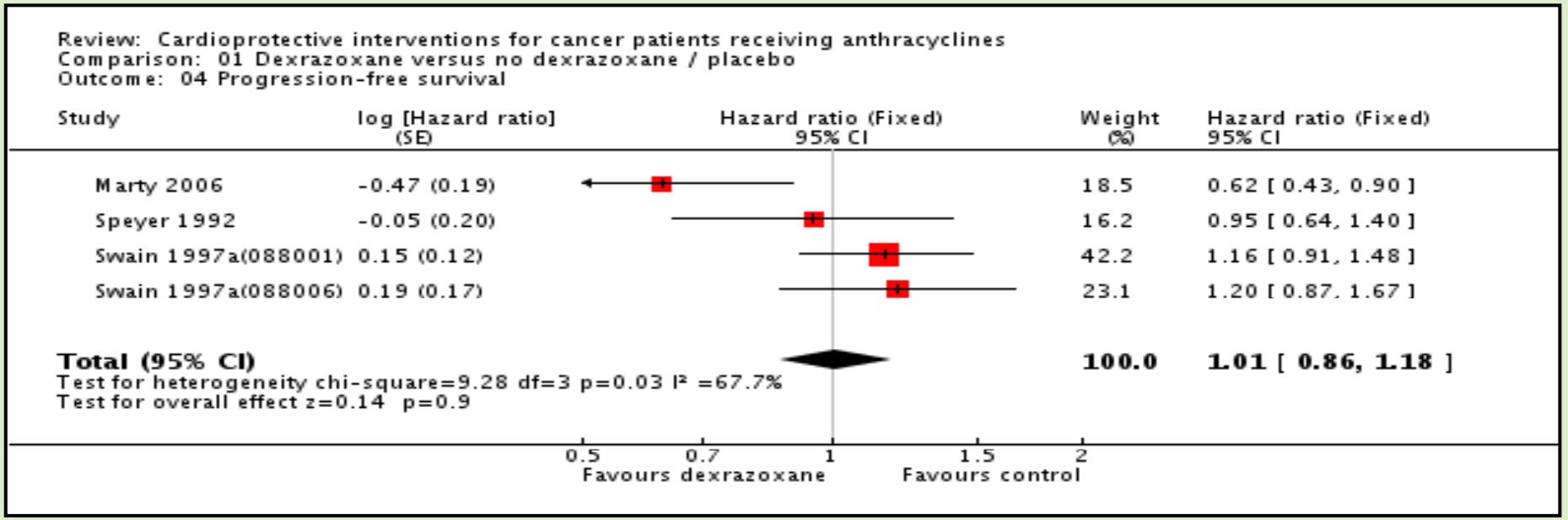
- ***Progression free survival*** - **The meta-analysis showed no significant difference between the dexrazoxane and control group (HR = 1.01, 95% CI 0.86 to 1.18, p = 0.89).**



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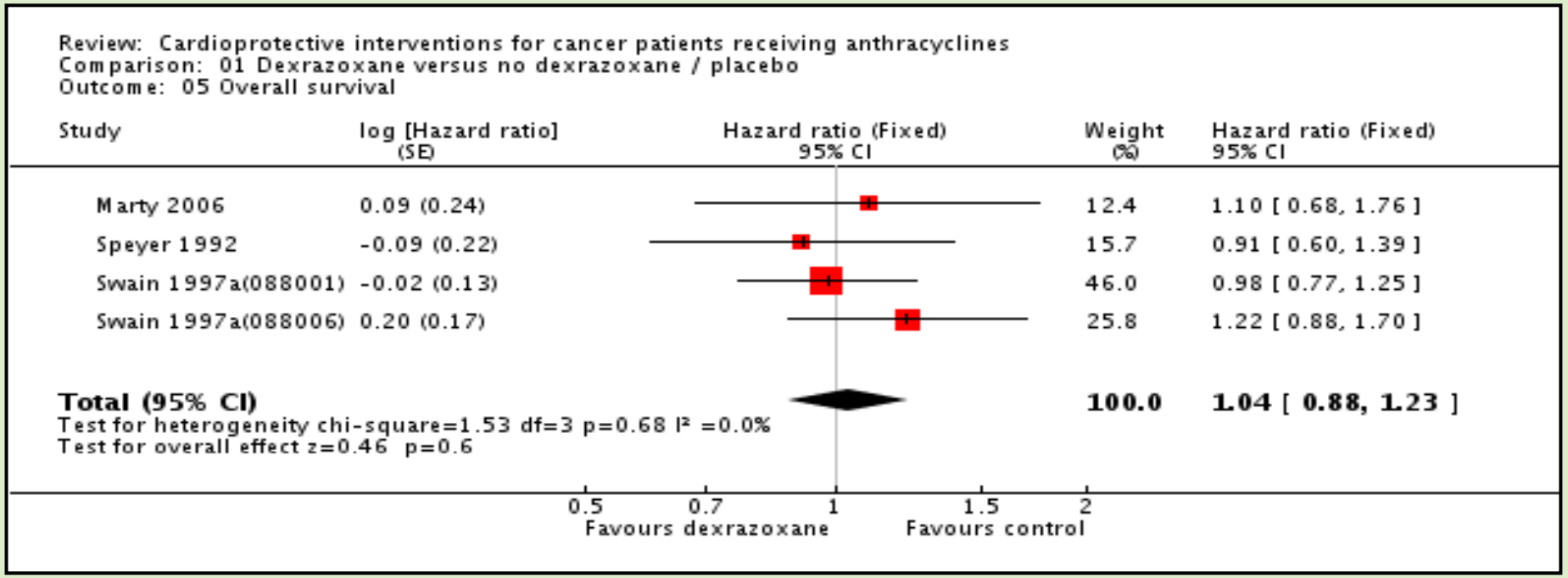
The Cochrane Library 2008, Issue 2

THE COCHRANE COLLABORATION®

- ***Overall survival*** **- The meta-analysis also showed no significant difference between the dexrazoxane and the control group (HR = 1.04, 95% CI 0.88 to 1.23, p = 0.65).**



The recommended use for Cardioxane – expert panel review :

Swain & Vici, J Cancer Res ClinOncol 2004

- ***ASCO guidelines gave great emphasis to trial published by Swain, in which tumor response was higher in placebo patients than cardioxane patients***

- **One randomised trial out of 10 has shown an effect on tumour response**
- **This one trial showed no effect on progression-free or overall survival**
- **None of the other trials showed an effect on tumour response, progression-free survival or overall survival**

The recommended use for Cardioxane – expert panel review :

Swain & Vici, J Cancer Res ClinOncol 2004

- **Dexrazoxane is an effective cardioprotector.**
- **Dexrazoxane does not interfere with anthracycline therapy.**
- **The cardiotoxic effect of anthracyclines starts from the first dose**
- **Dexrazoxane should be used from the first dose of anthracyclines**
- **Dexrazoxane should be given in patients with all tumor types receiving anthracyclines.**
- ***My own view:*** **Dexrazoxane is especially "cost-effective" in adjuvant/curative therapy reducing late cardiotoxicity**

Recommended use for Cardioxane:

(guideline for the undecided physician)

Risk Factors:

- **Age ≥ 65 years**
- **Prior anthracycline dose >150 mg/m2**
- **Low baseline LVEF (<50%)**
- **Trastuzumab treatment**
- **Taxane co-treatment**
- **Left chest or mediastinal irradiation**
- **Hypertension**
- **Diabetes**
- **Overweight**
- **IHD**

Cardioxane should be administered to all high-risk patients from the first dose of Anthracyclines

Recent Article:

Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia (ALL): long-term (10-year) follow-up of a prospective, randomised, multicentre trial

Steven E Lipshultz et al.
Lancet Oncol 2010; 11: 950–61

Doxorubicin cum. Dose=300 mg/m^2
Dexrazoxane given from 1st treatment at 10:1 mg ratio

Conclusion: Dexrazoxane provides long-term cardioprotection without compromising oncological efficacy in doxorubicin-treated children with ALL.

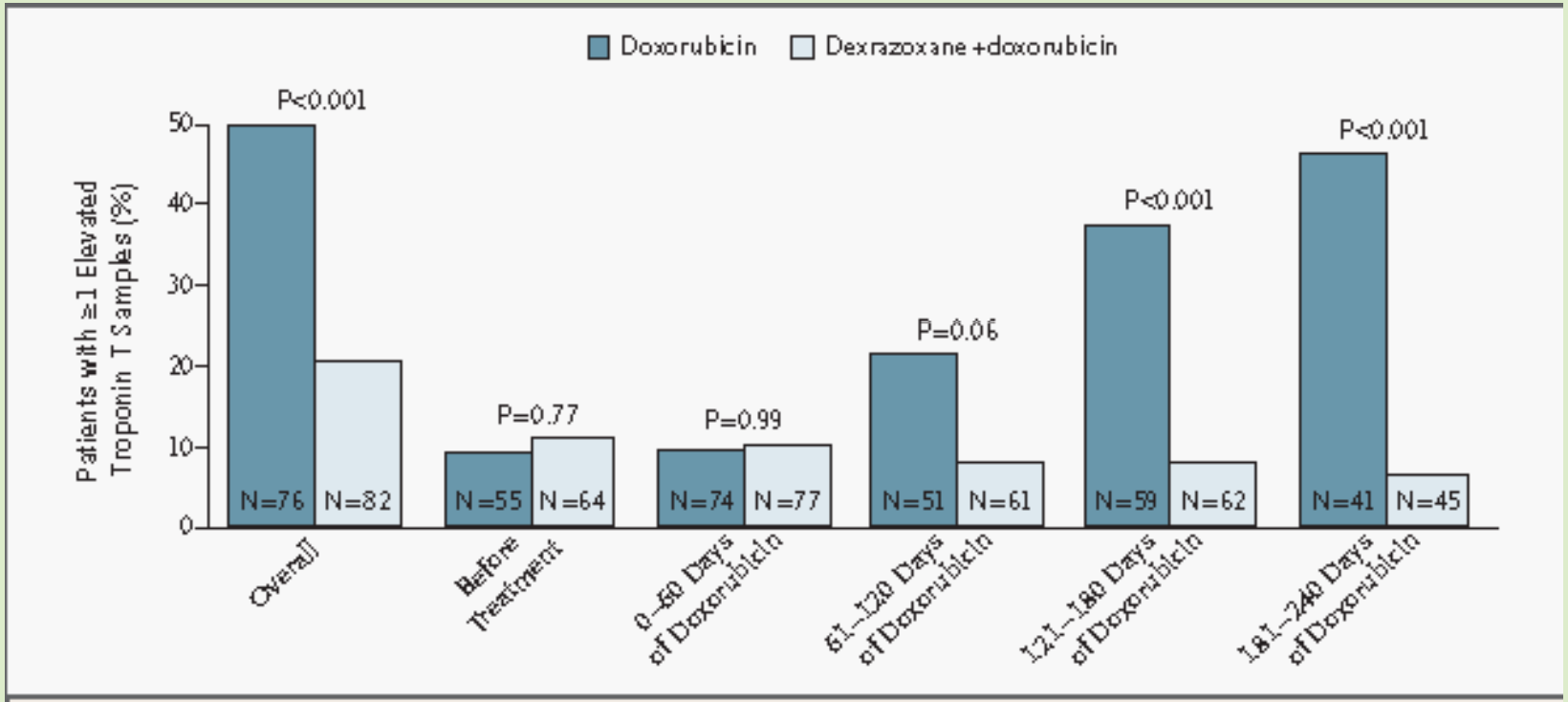


Figure 2. Percentage of Patients with at Least One Elevated Cardiac Troponin T Level Overall, before Treatment with Doxorubicin, and during Treatment.

An elevated level of troponin T was defined as one that exceeded 0.01 ng per milliliter. The number of patients in whom troponin T was measured at least once during the specified intervals is shown in each bar.

Lipshultz et al, 2004/2010

[CANCER RESEARCH 42, 4734-4739, November 1982]
0008-5472/82/0042-OOOOS02.00

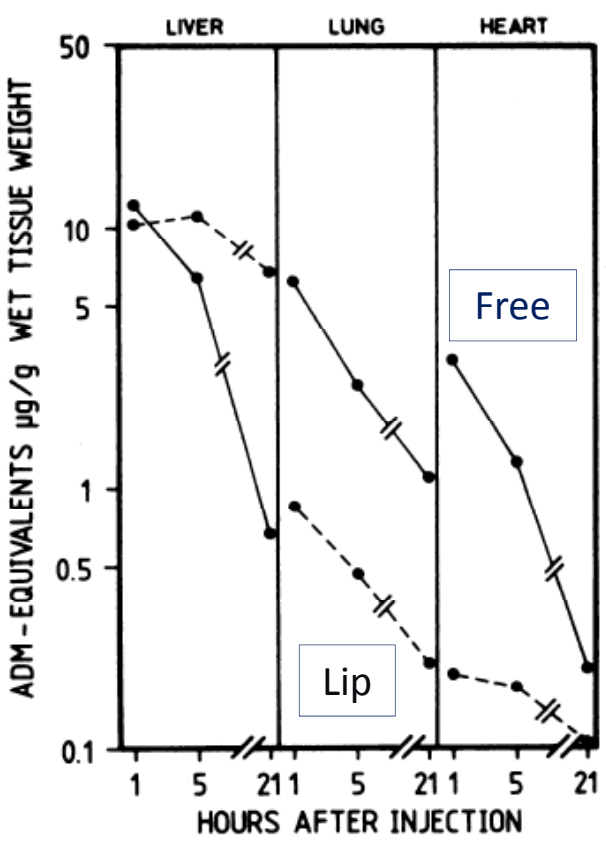
Liposomes as in Vivo Carriers of Adriamycin: Reduced Cardiac Uptake and Preserved Antitumor Activity in Mice

A. Gabizon, A. Dagan, D. Goren, Y. Barenholz, and Z. Fuks

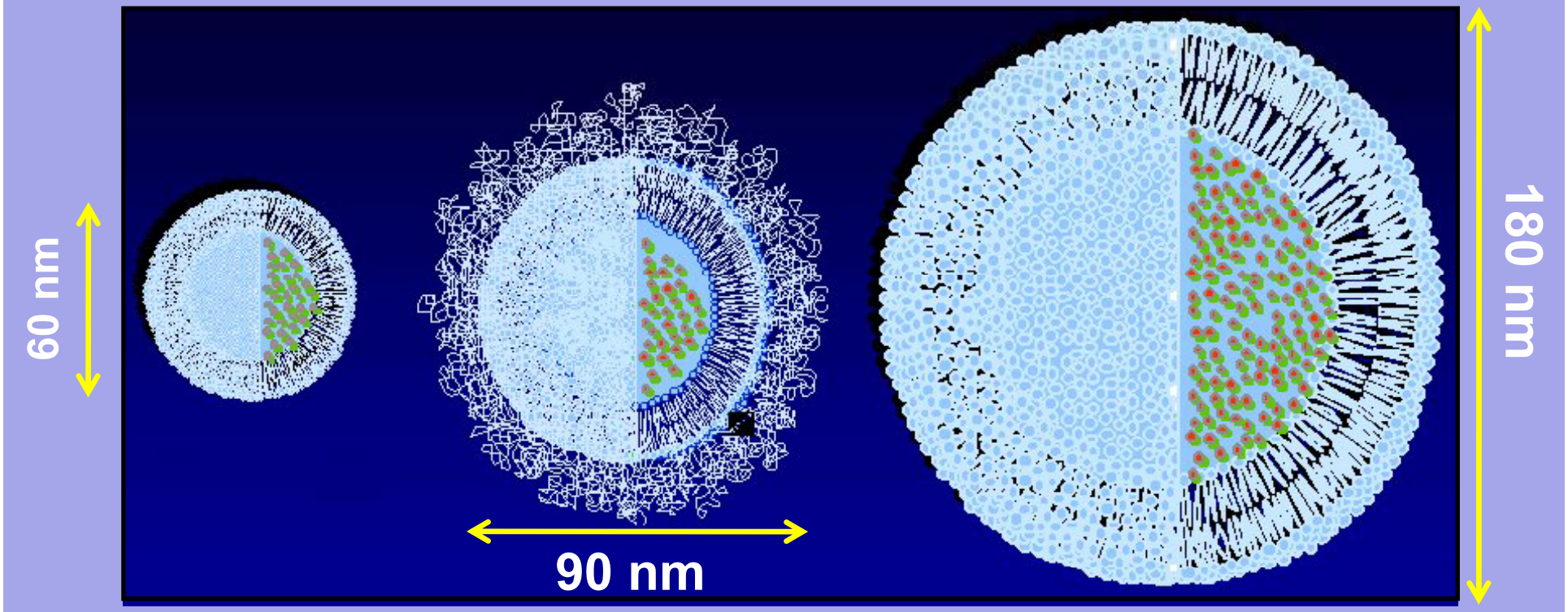
Department of Radiation and Clinical Oncology, Hadassah University Hospital [A. G., D. G., Z. F.], and Department of Biochemistry, Hebrew University-Hadassah Medical School [A. D., Y. BJ, Jerusalem, Israel

- Liposomes cannot extravasate across the tight junctions of microvessels of the heart muscle, thus preventing their doxorubicin payload from reaching the heart.

- Liposomes are taken up by tissues rich in macrophages in contact with blood stream (RES) such as liver and spleen where drug accumulates .



Schematic Comparison of Liposome Morphology among Liposomal Anthracyclines



DaunoXome

Doxil/Caelyx (Stealth liposome)

D-99 (Myocet)

The use of cardiac biopsy to demonstrate reduced cardiotoxicity in AIDS Kaposi's sarcoma patients treated with pegylated liposomal doxorubicin
Berry, G et al., Ann Oncol 9: 711-716,1998.

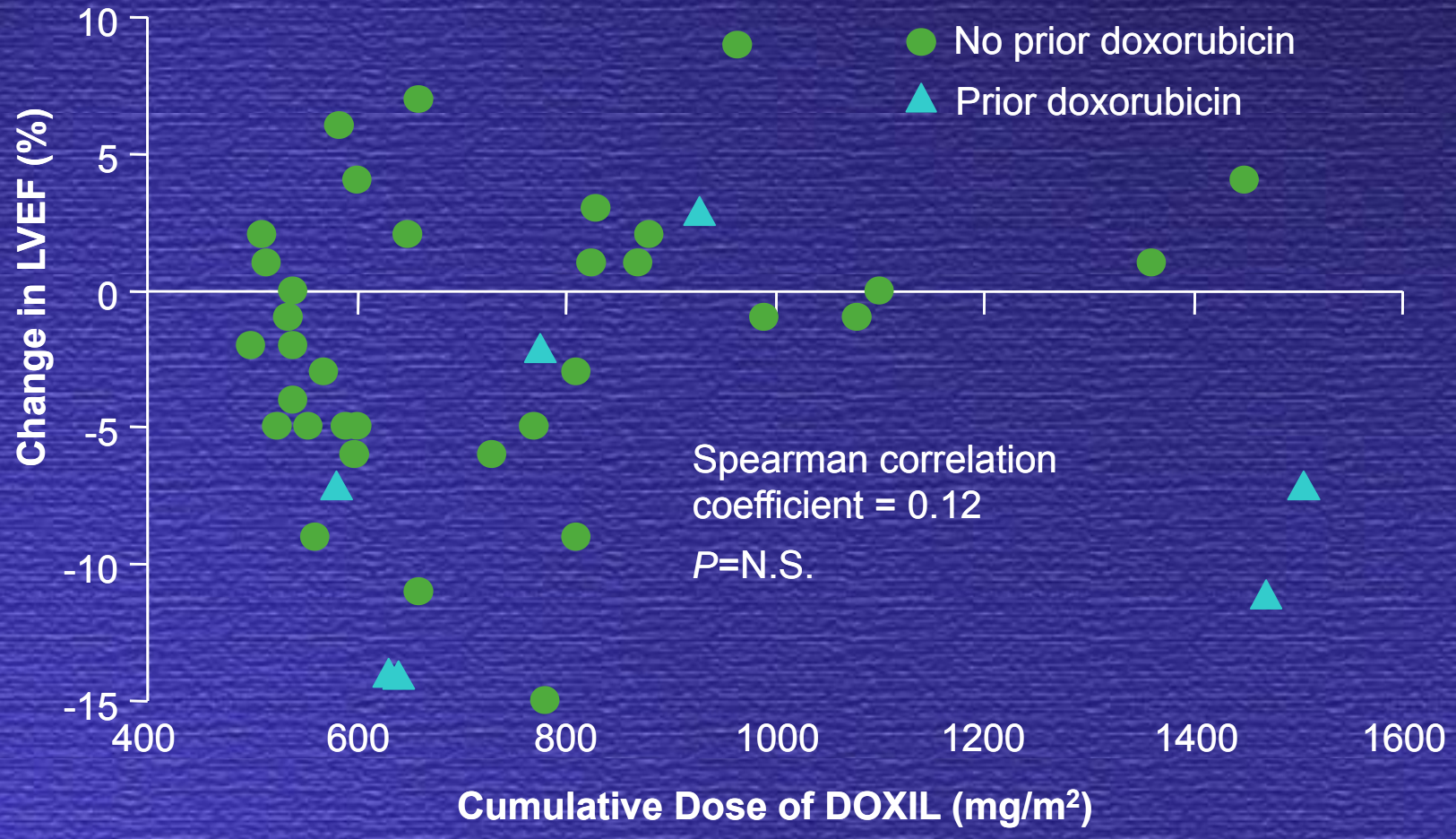
DOXIL: Reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2
Safra T, et al. Ann Oncol. 2000;11:1029-1033

Cardiac safety of pegylated liposomal doxorubicin demonstrated by endomyocardial biopsy in patients with advanced malignancies.
Gabizon A, et al. Cancer Invest. 2004;22(5):663-9.

Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX™/Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer
O'Brien, Wigler et al., Ann Oncol (2004) 15 (3): 440-449.

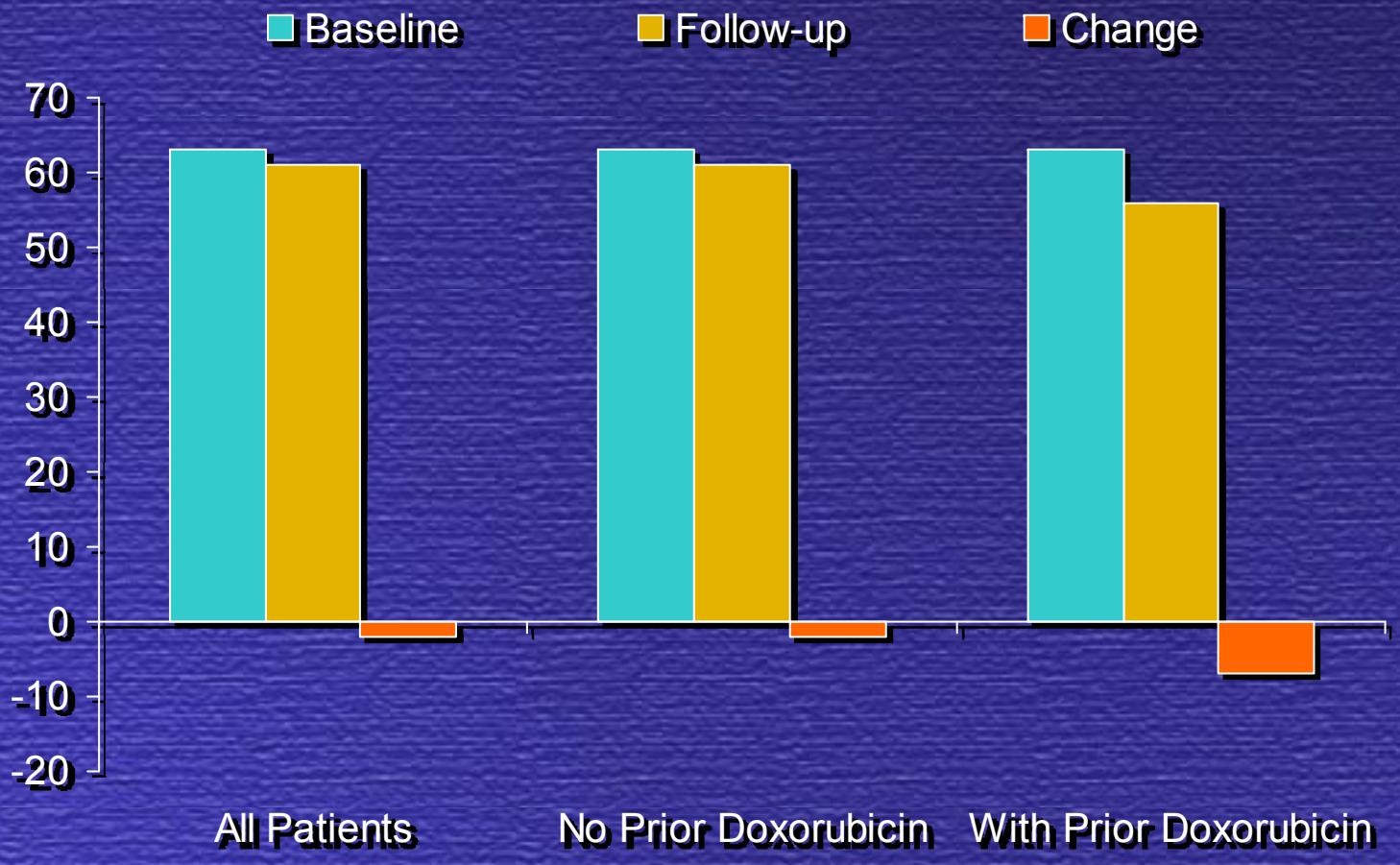
Monitoring long-term treatment with pegylated liposomal doxorubicin: how important is intensive cardiac follow-up?
Grenader T. et al. Anticancer Drugs. 2010 Oct;21(9):868-71

No Change in LVEF With Cumulative Dose of DOXIL



Safra T, et al. *Ann Oncol*. 2000;11:1029-1033.

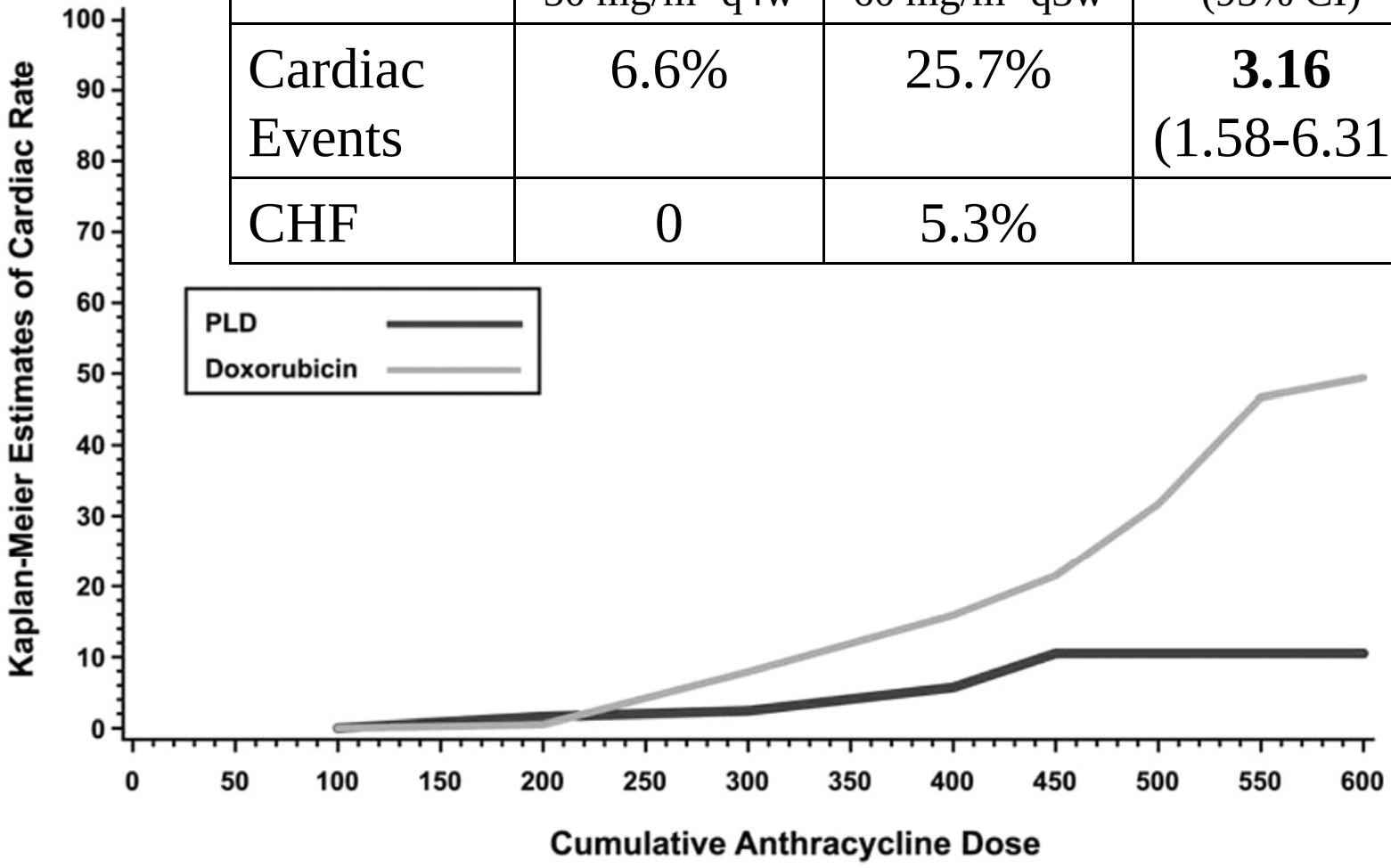
MUGA Results



Safra T, et al. *Ann Oncol*. 2000;11:1029-1033.

Reduced rate of cardiac events with DOXIL (PLD) vs doxorubicin

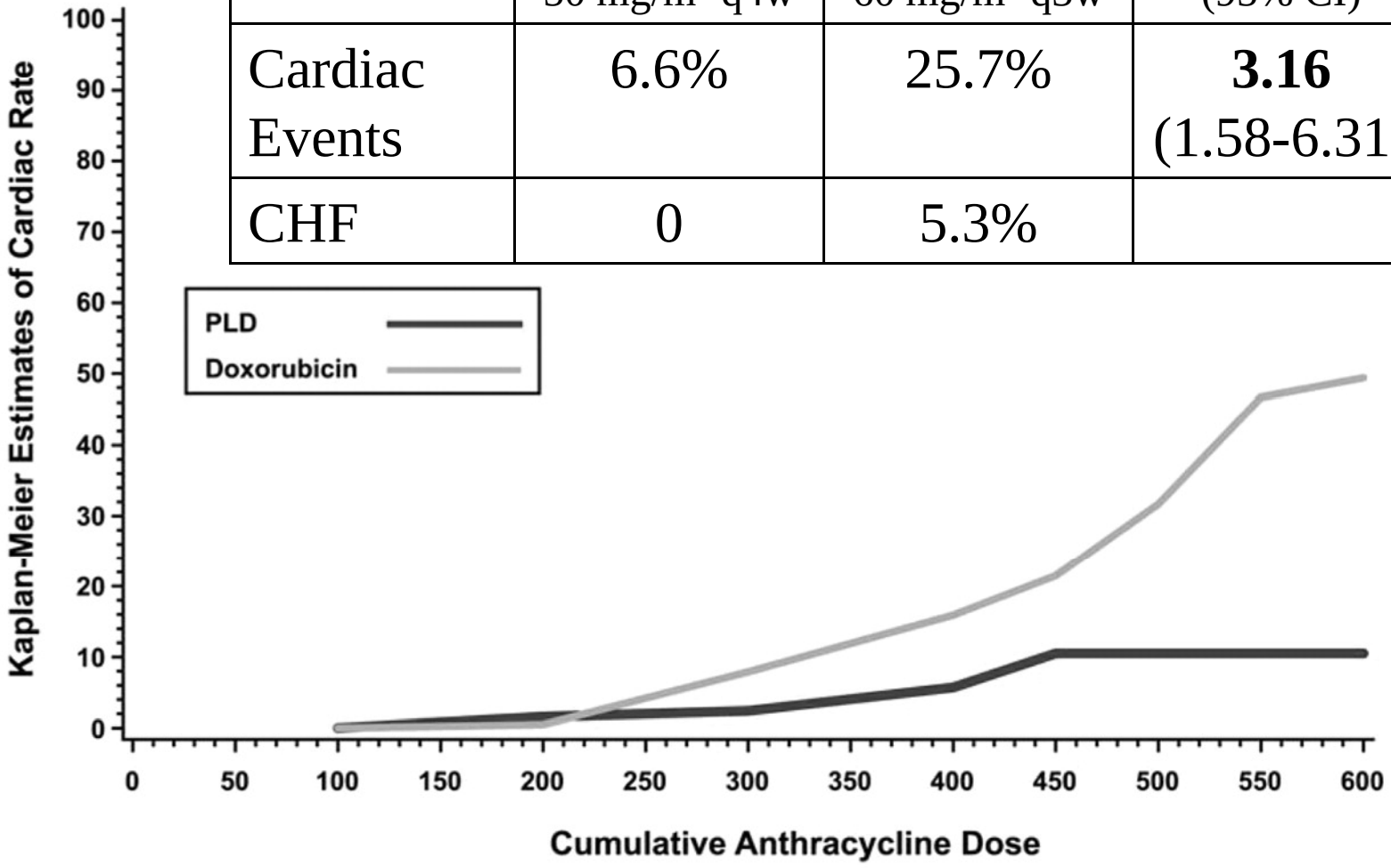
	PLD 50 mg/m^2 q4w	Doxorubicin, 60 mg/m^2 q3w	Hazard Ratio (95% CI)
Cardiac Events	6.6%	25.7%	**3.16** (1.58-6.31)
CHF	0	5.3%	



O'Brien M E R et al. Ann Oncol 2004;15:440-449

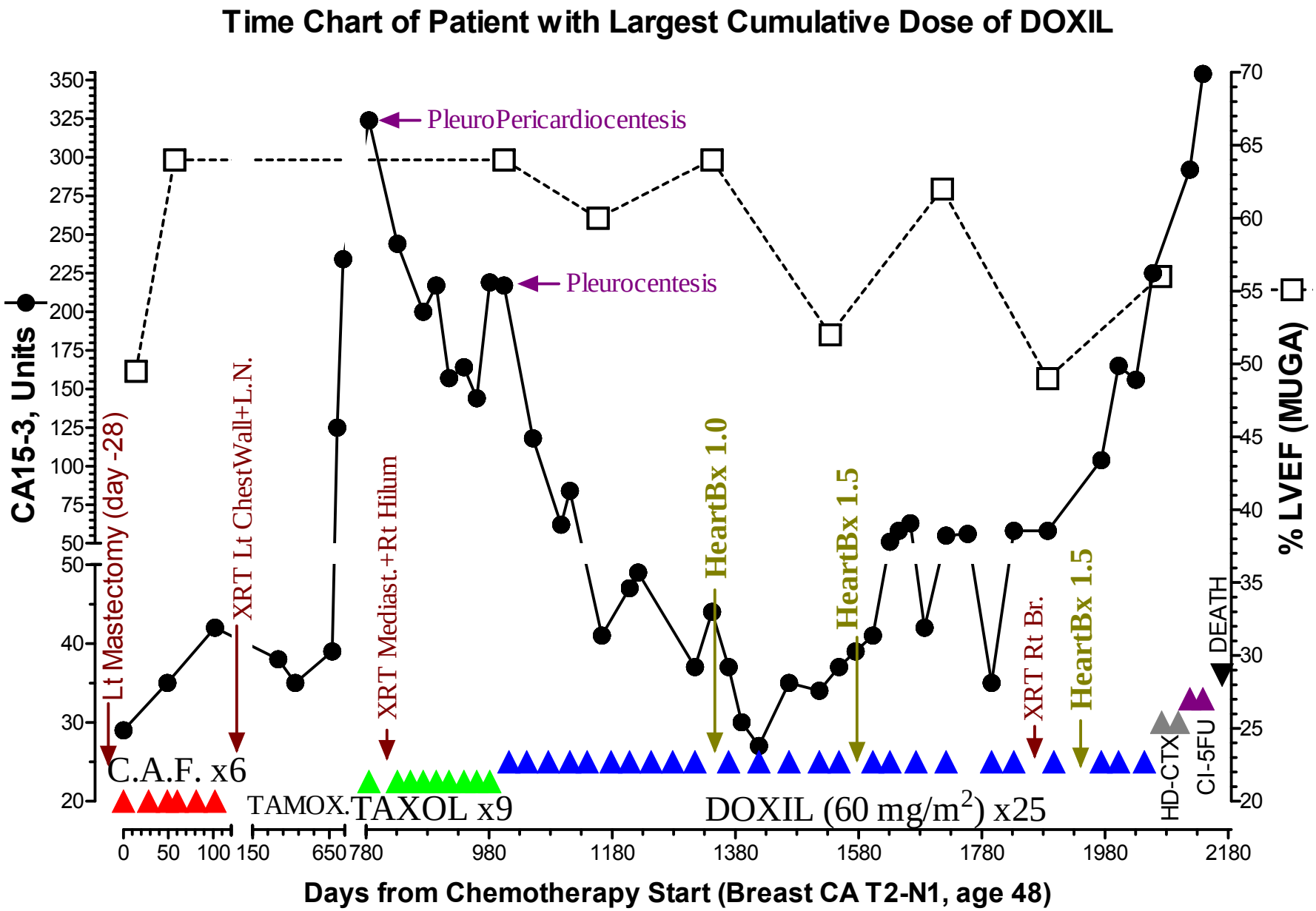
Reduced rate of cardiac events with DOXIL (vs doxorubicin)

	PLD 50 mg/m^2 q4w	Doxorubicin, 60 mg/m^2 q3w	Hazard Ratio (95% CI)
Cardiac Events	6.6%	25.7%	**3.16** (1.58-6.31)
CHF	0	5.3%	



O'Brien M E R et al. Ann Oncol 2004;15:440-449

Annals of Oncology


Time Chart of Patient with Largest Cumulative Dose of DOXIL
CA15-3, Units
% LVEF (MUGA)
PleuroPericardiocentesis
Pleurocentesis
Lt Mastectomy (day -28)
XRT Lt ChestWall+L.N.
XRT Mediast.+Rt Hilum
HeartBx 1.0
HeartBx 1.5
XRT Rt Br.
HeartBx 1.5
DEATH
HD-CTX
CI-5FU
C.A.F. x6
TAMOX.
TAXOL x9
DOXIL (60 mg/m2) x25
Days from Chemotherapy Start (Breast CA T2-N1, age 48)

Issues for Discussion

- Definition of Patients at increase cardiac risk
- Checking Troponin levels to detect patients at increased risk of cardiac toxicity
- Use of Cardioxane in Adjuvant AC
- DOXIL and Herceptin as a safe combination as indicated by recent studies in MBC
- Doxil testing in Adjuvant Therapy
- Other drugs that may attenuate cardiotoxicity: ACE inhibitors, Beta-blockers, Statins