Quali indicazioni all'impiego della doxorubicina liposomiale

4° INCONTRO ITALO-FRANCESE SUL CARCINOMA MAMMARIO:
problematiche attuali

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Background

- Conventional anthracyclines are the most widely used agents to treat breast cancer in the adjuvant setting, as well as in metastatic disease.
- Doxorubicin- based regimens have demonstrated benefits in terms of ORR, TTP, and OS.
- Despite its excellent antitumor activity, however, conventional doxorubicin has a relatively low therapeutic index, and its use is limited by **acute side effects**, as myelosuppression, alopecia, acute nausea and vomiting, stomatitis, cardiac events (LVD, myocarditis, arrhythmia)
- **Cumulative cardiotoxicity** is a major concern, leading to potentially fatal congestive heart failure.

Anthracycline-induced cardiotoxicity

- Cardiotoxicity occurs when **metabolic free radicals cause lipid peroxidation**.
- Initially, damage to the heart is subclinical; however, continued treatment will lead to progressive **myocyte damage**. The resulting cumulative cardiac dysfunction may become evident during therapy or subsequently in months or years after the final doxorubicin dose.
- Several factors may potentially increase the patient's risk of developing anthracycline-induced cardiotoxicity:

  higher cumulative anthracycline dose

  increased rate of drug administration

  advanced or very young age

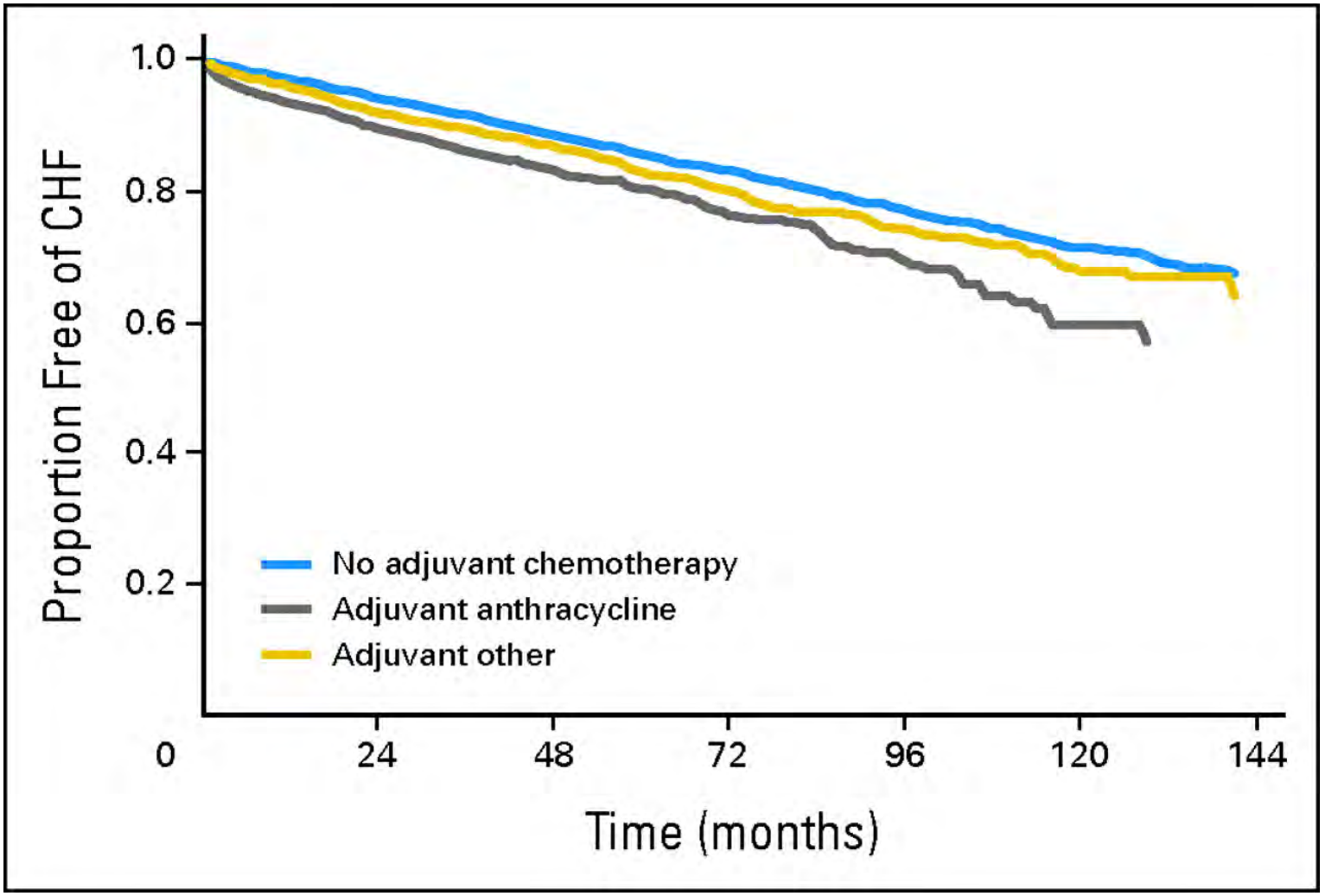
  mediastinal radiation

  female gender

  preexisting heart disease

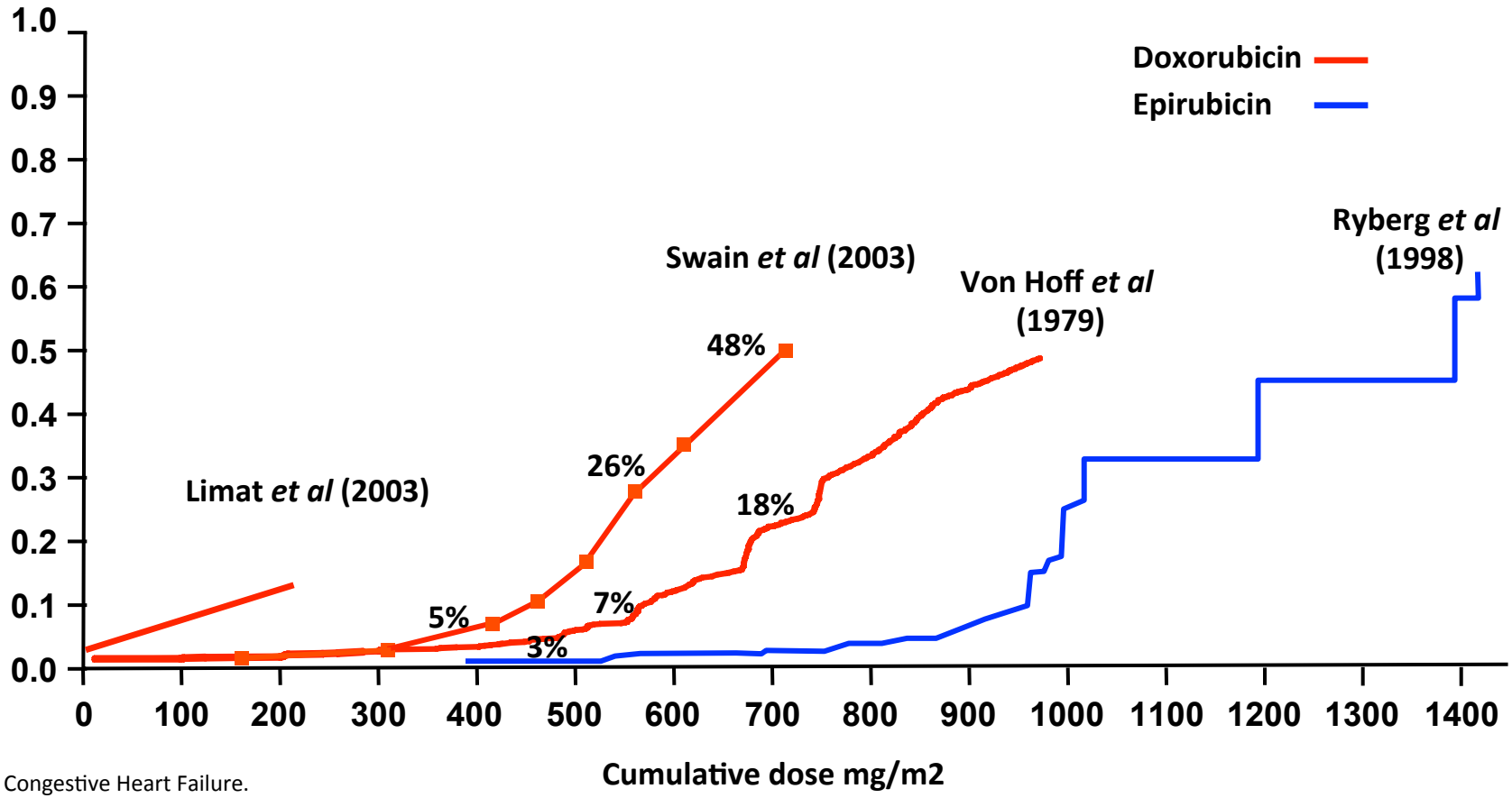
  hypertension.

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



Pinder M C et al. JCO 2007;25:3808-3815

Risk of anthracycline-related CHF



CHF: Congestive Heart Failure.

Definition of cardiotoxicity based on the mechanisms and reversibility

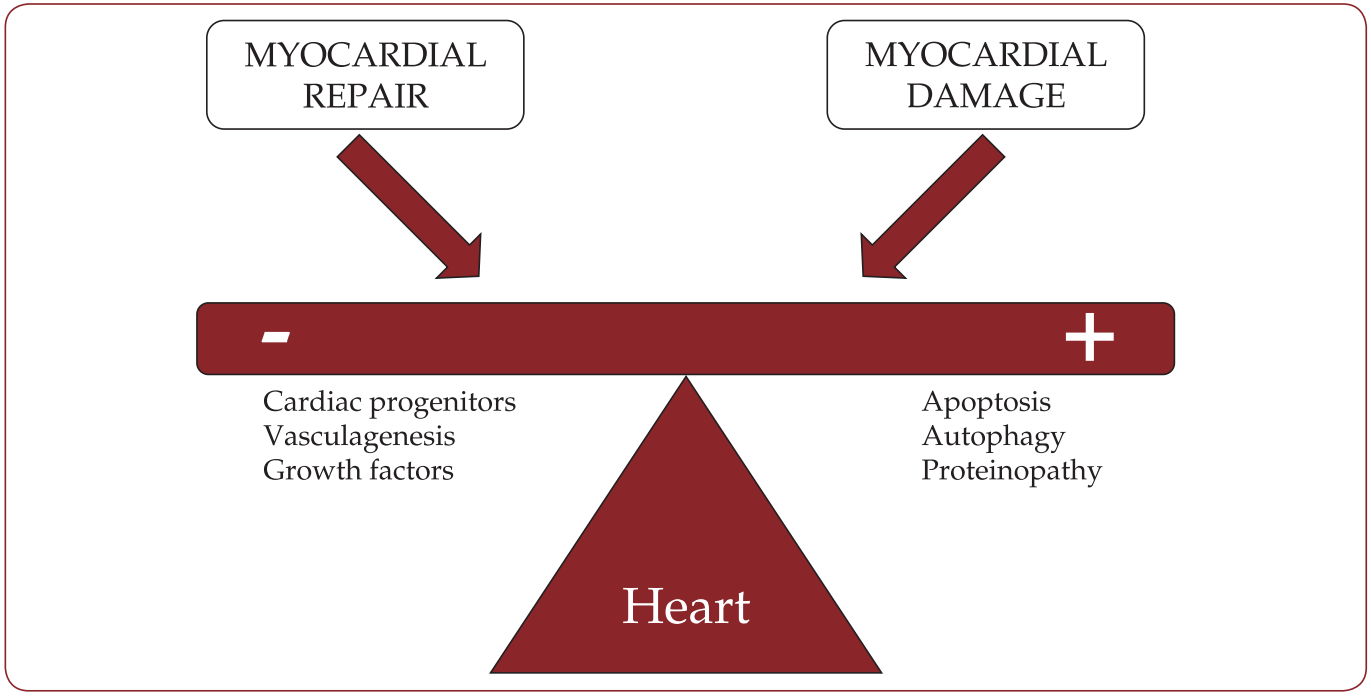


FIGURE 1. The direct effects on the myocardium of the chemotherapeutical drugs leading to cardiotoxicity (8,21).

	Type I (anthracycline-like)	Type II (trastuzumab-like)
Cellular mechanism	Cells death	Cells dysfunction
Dose related	Cumulative	Not-cumulative
Reversibility	Permanent	Reversible

Florescu, MAEDICA 2013

liposomal anthracyclines

- Liposome-based drug delivery systems are able to modify the pharmacokinetics and pharmacodynamics of cytostatic agents, enabling to increase the concentration of the drug released into the neoplastic tissue and, at the same time, reducing the exposure of normal tissue to the drug.
- There are several liposome-encapsulated doxorubicin formulations available which show different pharmacological characteristics. The most commonly used are liposomal doxorubicin (Myocet®, LD) and pegylated liposomal doxorubicin (Caelyx®, PLD).

RCTs of liposomal anthracyclines vs. conventional anthracyclines

Author	Trial phase	Treatment regimen	Patients' characteristics	PFS	OS	RR	Toxicity
O'Brien et al. [33]	III	PLD (50 mg/m^2/4w) versus ADR (60 mg/m^2/3w)	Stage IV	6.9 m versus 7.8 m	21 m versus 22 m	33% versus 38%	Cardiac: 4.7 versus 19.6% CHF: 0% versus 4%
Harris et al. [34]	III	LD (75 mg/m^2/3w) versus ADR (75 mg/m^2/3w)	Stage IV (17% ADR previous)	3.8 m versus 4.3 m	16 m versus 20 m	26%	Cardiac: 13 versus 29% CHF: 5.9 versus 15% Billingham > 2.5: 26 versus 71%
Batist et al. [35]	III	LD (60 mg/m^2) + CTX (600 mg/m^2) versus ADR (60 mg/m^2) + CTX (600 mg/m^2)	Stage IV (10% ADR previous) (30% CRF)	5.1 m versus 5.5 m	19 m versus 16 m		Cardiac: 6 versus 21% ($P < 0.05$) CRF: 0 versus 3.2%
Chan et al. [36]	III	LD (75 mg/m^2) + CTX (600 mg/m^2) versus EPI (75 mg/m^2) + CTX (600 mg/m^2)	Stage IV (No ADR previous)	7.7 m versus 5.6 m	18.3 m versus 16 m	46 % versus 39 %	Cardiac: 11 versus 10% No CRF
Sparano et al. [37]	III	Docetaxel (75 mg/m^2) versus Docetaxel (60 mg/m^2) + PLD (30 mg/m^2)	Stage IV (100% ADR previous)	7 m versus 9.8 m	20.6 m versus 20.5 m		Cardiac: 4 versus 5% PPS: 0 versus 24%

PLD: pegylated liposomal doxorubicin; LD: liposomal doxorubicin; ADR: adriamycin; EPI: epirubicin; CTX: cyclophosphamide; PFS: progression-free survival; OS: overall survival; RR: response rate; PPS: plantar-palmar syndrome; CHF: clinical heart failure; and CRF: cardiac risk factor.

Lao, J Drug Del, 2013

Liposome-Encapsulated Doxorubicin Compared with Conventional Doxorubicin in a Randomized Multicenter Trial as First-Line Therapy of Metastatic Breast Carcinoma

Chemotherapy (dose mg/m²)	N.	RR (%)	OS (months)	Cardiac Toxicity (%)	CHF (N)
Myocet® 75	108	26	16	13	2
vs					
Doxo 75	116	26	20	29	9
			ns	*p*= 0,0001	*p*= 0,0001

Harris et al, Cancer 2002

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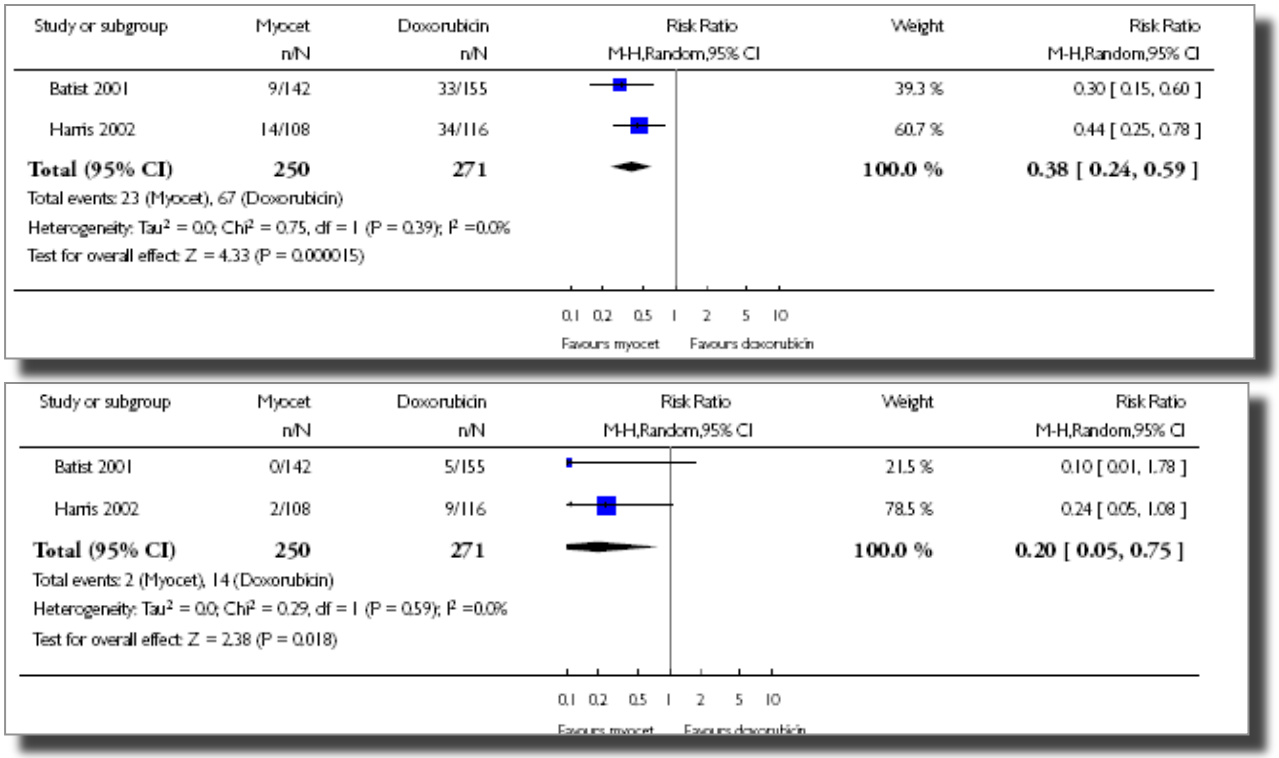
Reduced Cardiotoxicity and Preserved Antitumor Efficacy of Liposome-Encapsulated Doxorubicin and Cyclophosphamide Compared With Conventional Doxorubicin and Cyclophosphamide in a Randomized, Multicenter Trial of Metastatic Breast Cancer

Chemotherapy (dose mg/m²)	N.	RR (%)	OS (months)	Cardiac Toxicity (%)	CHF (N)
Myocet® 60 + Cy 600	142	43	19	6	0
vs					
Doxo 60 + Cy 600	155	43	16	21	5
			ns	*p*= 0,0001	*p*= 0,02

Batist et al, J Clin Oncol 2001

Different anthracycline derivates for reducing cardiotoxicity in cancer patients (Review)

van Dalen EC, Michiels EMC, Caron HN, Kremer LCM



Authors' conclusions

This systematic review of randomised trials provides evidence that nonpegylated liposomal anthracyclines reduced the overall risk of cardiotoxicity (RR = 0.38, $P < 0.0001$) and the risk of clinical heart failure (RR = 0.20, $P = 0.02$).

Published online: 10 MAY 2010

Phase III trial of liposomal doxorubicin and cyclophosphamide compared with epirubicin and cyclophosphamide as first-line therapy for metastatic breast cancer

Chemotherapy (dose mg/m²)	N.	RR (%)	OS (months)	Cardiac Toxicity (%)	CHF (N)
Myocet® 75 + Cy 600	80	46	18.3	11	7,7
vs					
Epi 75 + Cy 600	80	39	10	10	5,6
		ns	*P=0,005*	*P=0,007*	*P=0,02*

Chan et al, Annals Oncol 2004

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

Chemotherapy (dose mg/m²)	N.	RR (%)	OS (months)	Cardiac Toxicity (%)	CHF (N)
Caelix® 50	254	33	21	4,7	0
vs					
Adria 60	255	38	22	19,6	4
		ns	*ns*	*P=0,001*	*P=0,001*

O'Brien et al, Annals Oncol 2003

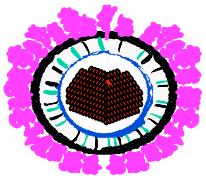
JOURNAL OF CLINICAL ONCOLOGY

Pegylated Liposomal Doxorubicin Plus Docetaxel Significantly Improves Time to Progression Without Additive Cardiotoxicity Compared With Docetaxel Monotherapy in Patients With Advanced Breast Cancer Previously Treated With Neoadjuvant-Adjuvant Anthracycline Therapy: Results From a Randomized Phase III Study

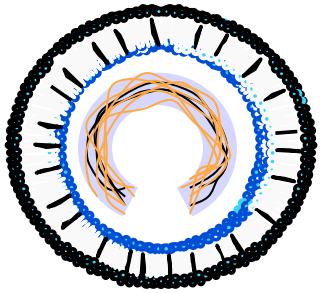
Chemotherapy (dose mg/m²)	N.	RR (%)	TTP (months)	Cardiac Toxicity (%)	PPS (%)
Docetaxel 75	373	26	7	4	0
vs					
Docetaxel 60 + Caelix® 30	377	35 *P=0,008*	9.8 *P=0,0001*	5 *ns*	24 *P=0,001*

Sparano et al J Clin Oncol 2009

PLD
Superficie in PEG (polietilenglicole)
~ 80 nm



LD
doxorubicina liposomiale
~ 150 nm



	PLD	LD
	cardiaco aumentato	metastatizzato della mammella
	50 mg/m² Non definito	3 settimane Definito
complessiva (ORR)	10 – 33%	26% – 43%
	Ridotta leucopenia e neutropenia	Ridotta neutropenia di grado 4 (p=0.02)
vs doxorubicina	Più casi di mucosite e stomatite (22%) Più casi di rash (25%) e eritema (18%)	Nessuno

1. O'Brien et al. *Ann Onco.* 2004; **2.** Keller et al. JCO 2004; **3.** Batist G et al. J Clin Oncol 2001; **4.** Harris L et al. Cancer. 2002

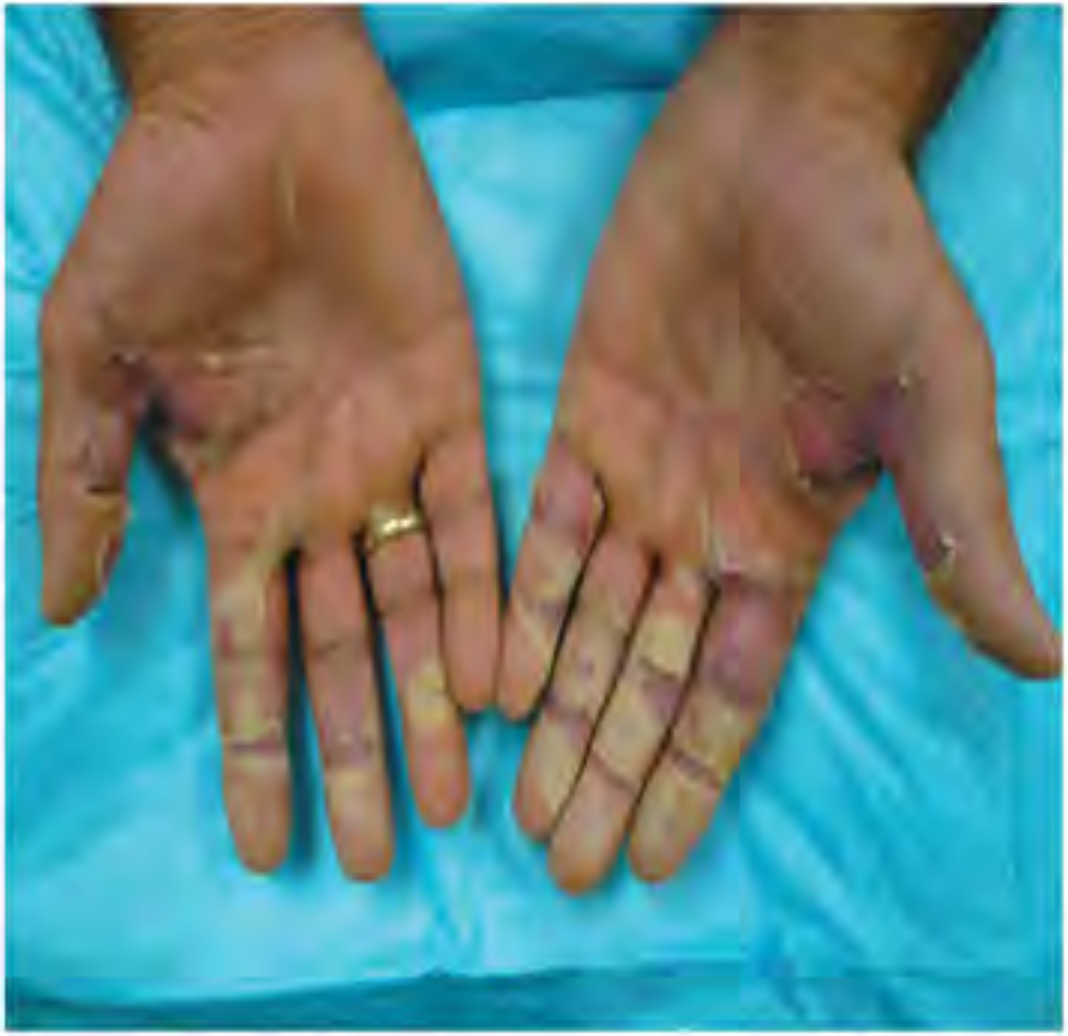


FIGURE 13: Pegylated doxorubicin and capecitabine hand-foot syndrome: Painful erythema, edema, and sensation of tightness and cracking in the palms and soles occurs in up to 30% of patients. Treatment consists of topical ammonium lactate 12%, and topical/oral steroids (dexamethasone at 8 mg bid for 5 days from day 1, followed by 4 mg bid for day 1, then 4 mg qd for 1 day).

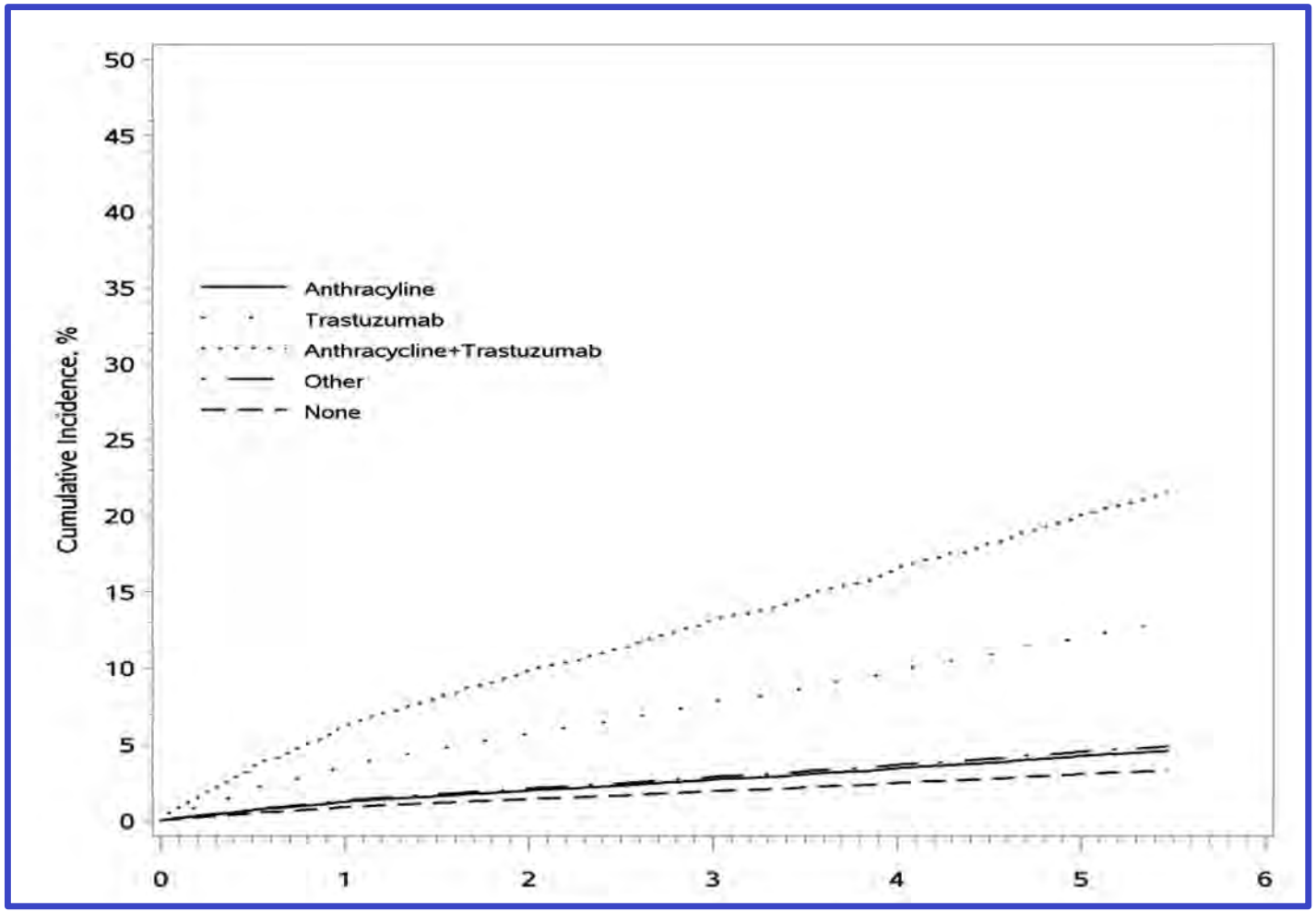
Liposomal Anthracyclines and Trastuzumab

- In HER2-postive breast cancer, the addition of trastuzumab to chemotherapy significantly increases response rate, time to progression, and overall survival compared with chemotherapy alone. However, when trastuzumab is combined with anthracyclines there is an increased risk of cardiac toxicity.
- Cardiotoxicity limited the use of anthracyclines in HER2-positive breast cancer, and in consequence non-anthracycline-based regimens such as TCH were designed in order to avoid late-toxicities, especially in adjuvant setting .
- As anthracyclines showed a high level of activity in this subgroup of patients, other strategies were developed also to design regimens using less cardiotoxic anthracyclines such as **epirubicin** (a less cardiotoxic analog than doxorubicin) at limited doses or **liposomal anthracyclines** in combination with trastuzumab.

Risk of Heart Failure in Breast Cancer Patients After Anthracycline and Trastuzumab Treatment: A Retrospective Cohort Study

Erin J. Aiello Bowles, Robert Wellman, Heather Spencer Feigelson, Adedayo A. Onitilo, Andrew N. Freedman, Thomas Delate, Larry A. Allen, Larissa Nekhlyudov, Katrina A. B. Goddard, Robert L. Davis, Laurel A. Habel, Marianne Ulcickas Yood, Catherine McCarty, David J. Magid, Edward H. Wagner; for the Pharmacovigilance Study Team

J Natl Cancer Inst 2012;104:1293–1305



Phase I/II trials of NPLA (Myocet®) in combination with Trastuzumab:

Setting Autor	Treatment (dose mg/m^2)	N.	RR (%)	PFS (months)	Cardiac Toxicity (%)	CHF (%)
MBC anthra pretr. **Theodoulou 2002**	Myocet®70 q21+ Trastuzumab (w)	37	58	*nr*	37	5
LABC / MBC chemo naive **Cortes 2009**	Myocet®60 q21+ Paclitaxel 80 (w) + Trastuzumab (w) +	69	98	23	17	0
MBC 1st line **Venturini 2010**	Myocet®50 q21+ Docetaxel 75 q21 + Trastuzumab (w)	31	66	13	10	0
MBC 1st line **Amadori 2011**	Myocet®50 q21+ Docetaxel 30 (gg2,9) + Trastuzumab (w)	45	56	10.9	4	0

Phase I/II trials of PLA (Caelix®) in combination with Trastuzumab:

Setting Autor	Treatment (dose mg/m^2)	N.	RR (%)	PFS (months)	Cardiac Toxicity (%)	CHF (%)
MBC anthra pretr. Chia 2006	Caelix®50 q28 + Trastuzumab (w)	30	52	12	10	0
MBC anthra pretr Andreopoulou 2007	Caelix®40 q21+ Trastuzumab (w)	12	66	nr	25	0
MBC 1st line Stickeler 2009	Caelix®40 q28+ Trastuzumab (w)	16	50	9.6	0	0
MBC 1st line Wolff 2010	Caelix®30 + Docetaxel 60 q21 + Trastuzumab (w)	46	45	10.6	25	0

Liposomal Anthracyclines in metastatic setting

- In patients with metastatic breast cancer, liposomal anthracyclines have proven to be as effective and less toxic when compared face to face with conventional anthracyclines, allowing a longer period of treatment and a higher cumulative dose of the anthracyclines.
- The combined analysis of available data indicates an overall reduction in risk for both cardiotoxicity and clinical heart failure.
- The safety of liposomal anthracyclines endorsed its use in patients with some cardiac risk factors.

Liposomal Anthracyclines in combination with Trastuzumab:

- In HER2-positive breast cancer, the addition of trastuzumab to chemotherapy significantly increased response rate, progression-free survival, and overall survival.
- Initial studies demonstrated synergy when trastuzumab was combined with anthracyclines, but their excessive cardiac toxicity limited their use, and nonanthracycline therapeutic strategies were therefore designed.
- Liposomal anthracyclines have proven to be effective and safe when combined with trastuzumab both in advanced and early breast cancer. Of particular interest is the use of the combination of liposomal anthracyclines plus trastuzumab in patients with early and HER2-overexpressing breast cancer, as this is probably the subgroup that would benefit most from a treatment with anthracyclines.
- The potential clinical benefit of anthracyclines in this setting should be investigated in a clinical trial comparing a regimen with liposomal anthracyclines versus a nonanthracyclines combination.

Grazie per l'attenzione