PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

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Cardiotossicità da antracicline e farmaci biologici

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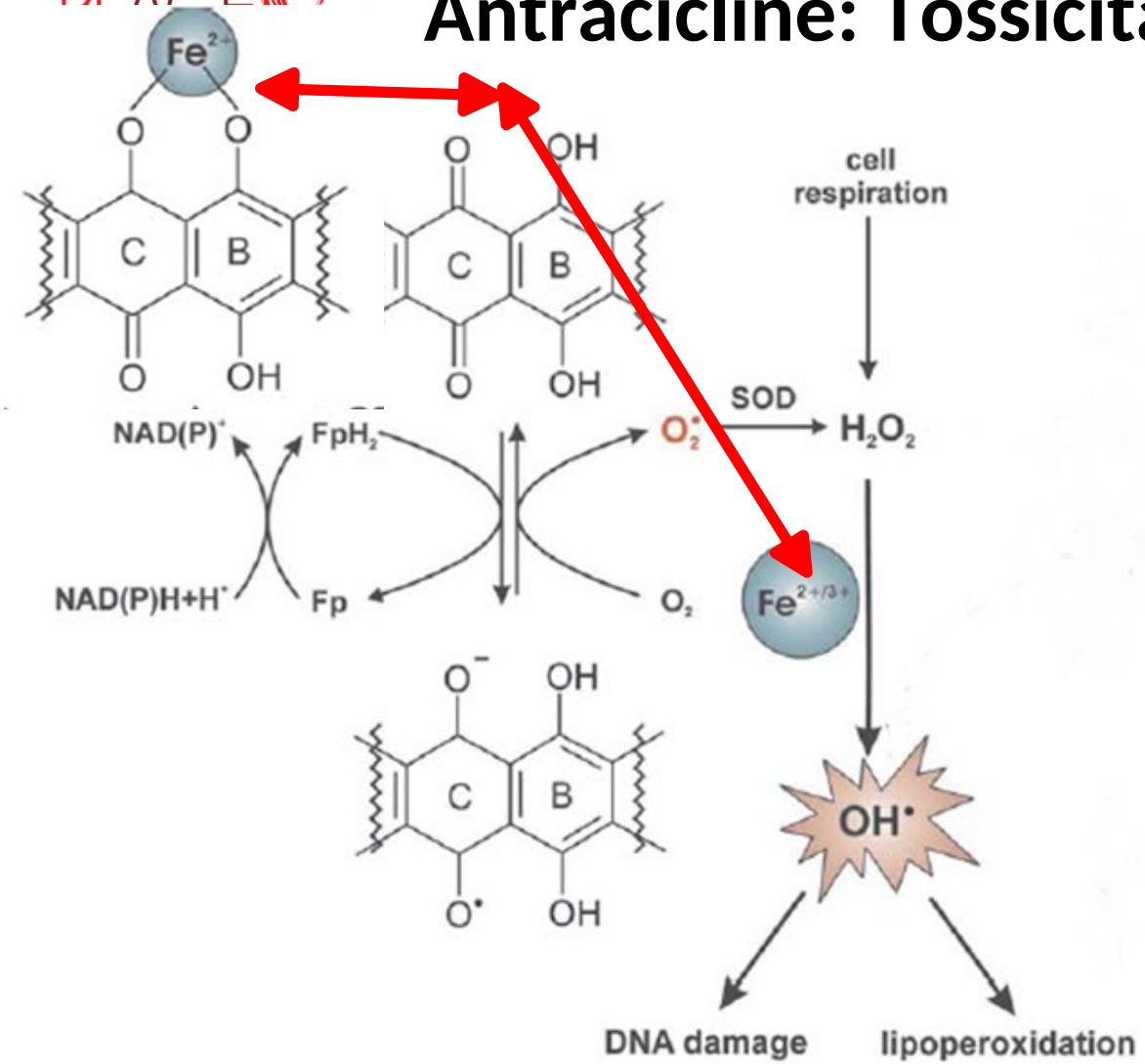
Antracicline: Tossicità classica

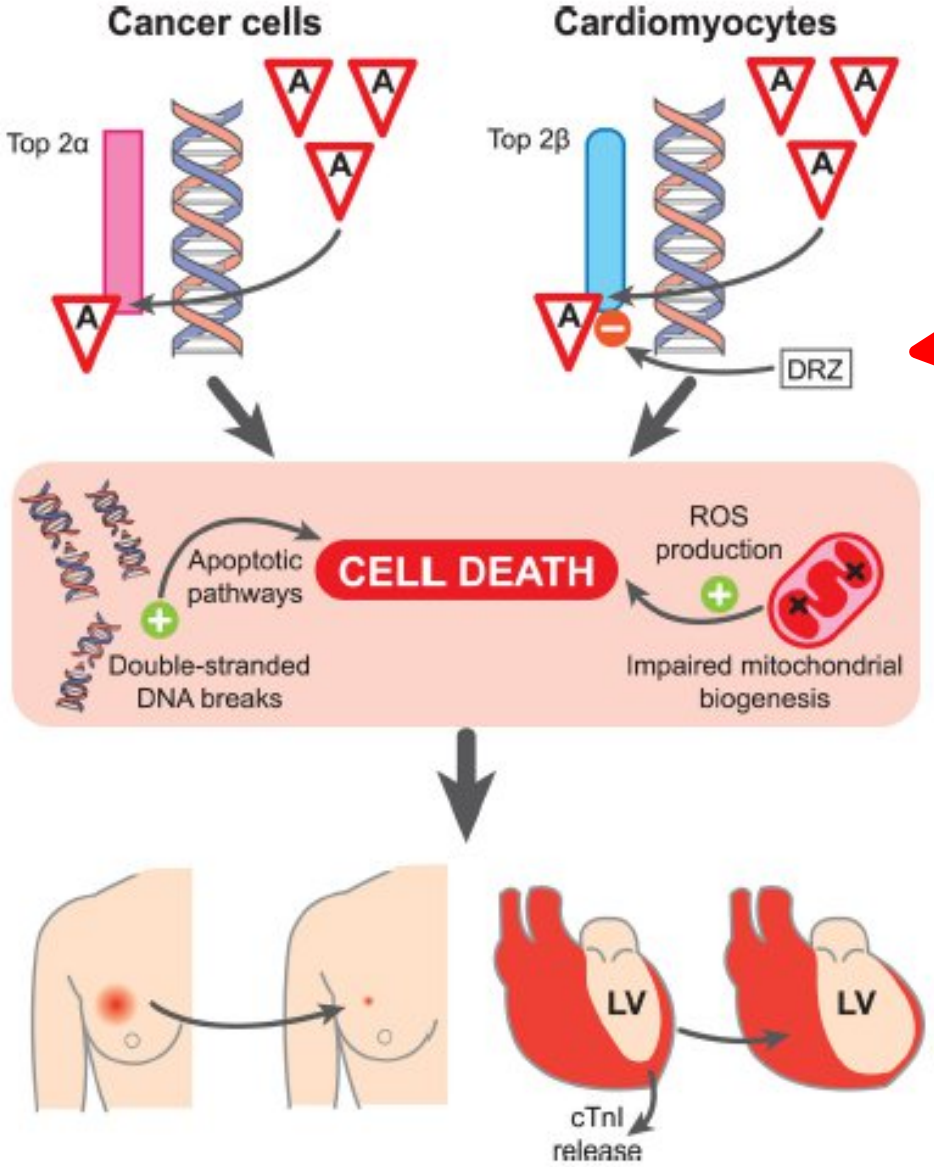


free iron accumulation within the myocardium seems to be a major determinant

anti-oxidants failed to provide therapeutic benefits in preclinical and clinical models, while iron chelators, such as dexrazoxane, appeared to be more promising.

Simunek et al, 2009 modificata

Altri meccanismi citotossici e cardiotossici



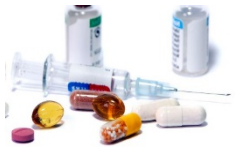
inhibition of anthracycline binding to Top 2β

Henriksen PA. Heart 2018;104:971–977

Tipi di cardiotossicità

Anthracycline-induced cardiotoxicity has traditionally been classified into :

- acute or early (during treatment),
- subacute (within a year of exposure),
- chronic (years after exposure) disease processes.



<u>Early manifestations</u>:
electrocardiographic abnormalities, arrhythmias, atrioventricular block, and a pericarditis myocarditis Syndrome
<u>Late clinical manifestations</u>:
symptoms and signs of HF such as dyspnea, fatigue, edema, and orthopnea.

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Fattori di rischio

- Older age (>65 years) or very young age (<4 years old),
- Female gender,
- Preexisting cardiovascular disorders,
- Hypertension, smoking, hyperlipidemia, obesity, diabetes, and high cumulative anthracycline exposure,
- Radiation therapy and use of trastuzumab.

Recognition of these risk factors, and response to them by using non-anthracycline chemotherapy when appropriate, has diminished the incidence of anthracycline-induced heart failure

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Identificazione dei pazienti a rischio (in funzione della dose)

- High-dose anthracycline (eg, doxorubicin ≥250 mg/m2, epirubicin ≥600 mg/m2)
- High-dose radiotherapy (RT; ≥30 Gy)

- Lower-dose anthracycline (doxorubicin <250 mg/m2 , epirubicin <600 mg/m2) in combination with lower-dose RT (<30 Gy)
- Lower-dose anthracycline or trastuzumab alone, and presence of any of the following risk factors:
  - ≥2 risk factors including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age at cancer treatment
  - Compromised cardiac function at any time before or during treatment
  - Treatment followed by trastuzumab (sequential therapy)

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Approccio alla prevenzione

Collaboration between the treating oncologist, internist, cardiologist and pharmacist

Baseline clinical cardiovascular assessment, including physical examination and an echocardiogram prior to initiation of anthracyclines.

- ***Current or past heart failure***
  - borderline reduced LVEF (LVEF >40 but <50),
  - or LVEF ≤40 percent,

    anthracycline chemotherapy should generally be avoided

- ***No current or past heart failure***, LVEF >40 and <50 percent:

  a risk-benefit analysis of available treatment options should be performed.

  If proceed with anthracycline therapy then apply specific measures:
  - blood pressure control in hypertensive patients,
  - discontinuation of anthracyclines if the LVEF decreases by more than 10 absolute percentage points from baseline

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Modifiche alla chemio con antracicline

- All patients with HF and/or a significant decline in LVEF exclude causes other than anthracycline cardiotoxicity (myocardial infarction/ischemic heart disease, stress cardiomyopathy, myocarditis, or infiltrative disease)

- For patients who require modification of their treatment due to significant decline in LVEF after having started anthracycline based treatment, generally avoid dose reduction of anthracyclines, instead opting for non-anthracycline-based alternatives

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Modifiche alla chemio con antracicline, interventi farmacologici

- **significant decline in LVEF and/or HF after initiation of anthracycline therapy:**

  - For patients who develop HF
    - with LVEF <50 percent,
    - or a decline in LVEF to under 40 percent,
    - or a significant decline in EF (15 absolute percentage points) to <50 percent,

    we hold anthracyclines, **treat with an ACE inhibitor (or ARB) plus beta blocker (**carvedilol or nebivolol).
    Consider utilize a **non-anthracycline-based regimen for future treatment cycles.**

  - For asymptomatic patients with a decline in LVEF of at least 10 percentage points to <50 percent but >40 percent, **consider treatment with an ACE inhibitor (or ARB) plus beta blocker for secondary prevention.**

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Modifiche alla chemio con antracicline

- Infusional rather than bolus regimens of anthracyclines

- Dexrazoxane is approved for use in metastatic breast cancer to lower the risk of cardiomyopathy in patients who have received more than 300 mg of doxorubicin and are felt to derive significant benefit from continuing therapy.

- If high cumulative doses of anthracyclines (comunque limitare le dosi doxo a 450-550 mg/m2) , a liposomal formulation of anthracycline may limit cardiotoxicity.

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Doxorubicine «protette» autorizzate

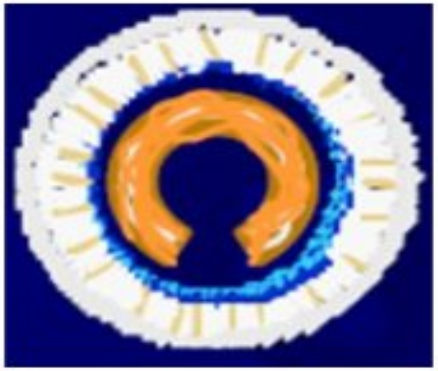
-Si distribuiscono prevalentemente nei tessuti ricchi di macrofagi

-Rilascio graduale del farmaco

-Scarsa diffusione attraverso i vasi cardiaci

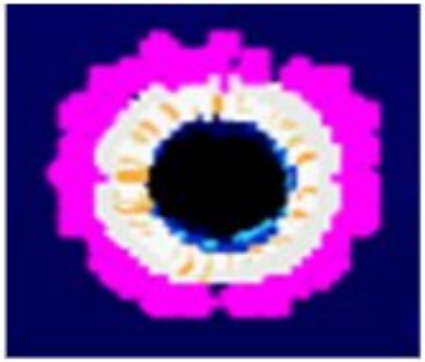
Formulazioni disponibili

–Doxorubicina liposomiale



Diametro 150 nm

–Doxorubicina liposomiale pegilata



Diametro 80 nm

Cardiotossicità da anticorpi monoclonali tipo II (biologici, trastuzumab)

Type I, associated with the anthracyclines, results in myocyte destruction and clinical heart failure.

Type II, associated with a loss of contractility and is more likely to be reversible.

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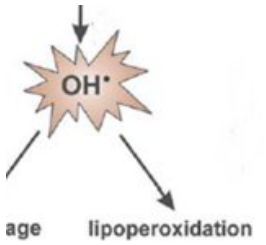
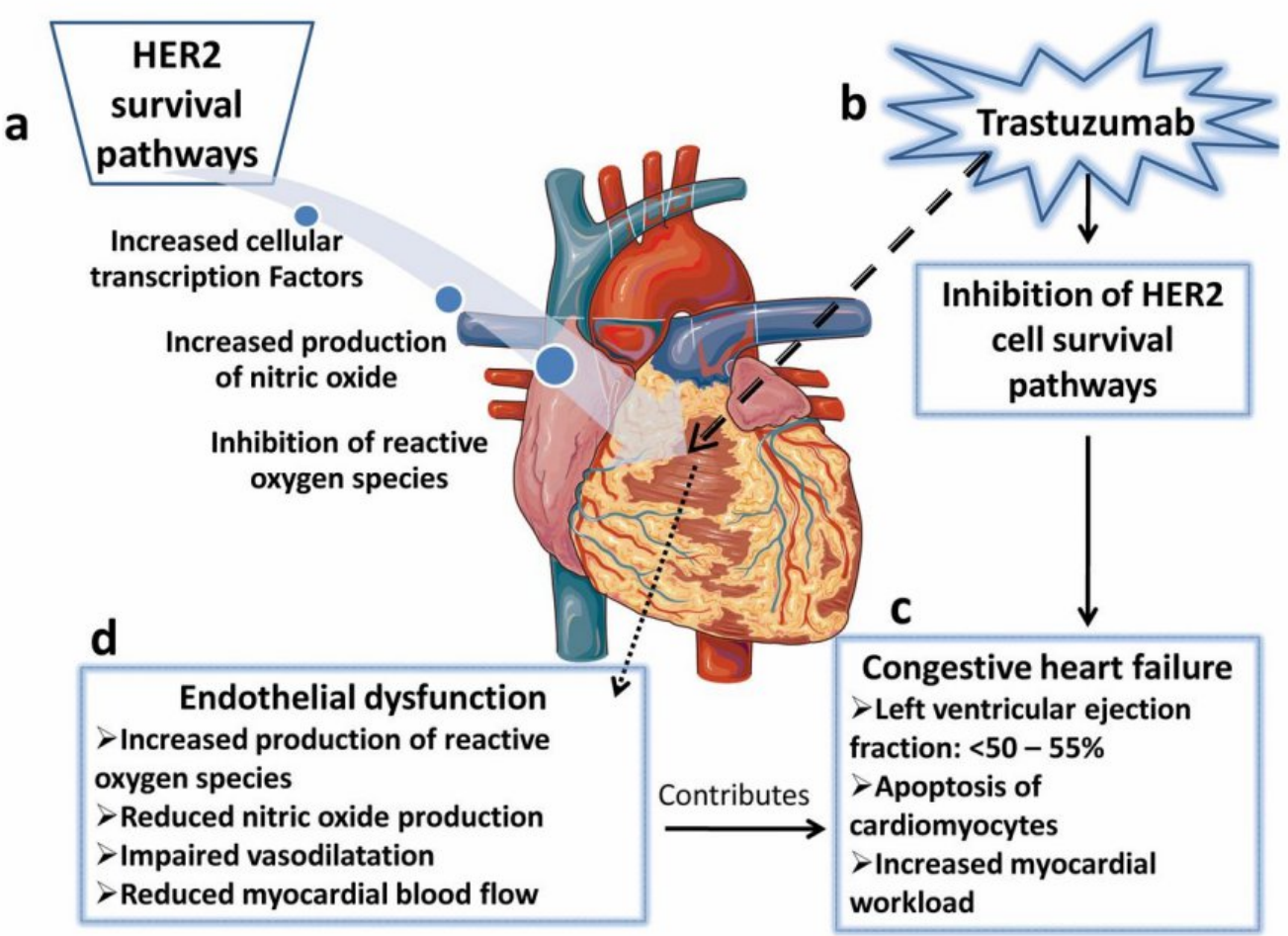
Trastuzumab sopprime il segnale ErbB2 e può accelerare il degradamento delle proteine sarcomeriche indotto dalle antracicline





Endothelial Dysfunction as a Determinant of Trastuzumab-mediated Cardiotoxicity in Patients with Breast Cancer
AAMER SANDOO, GEORGE D. KITAS and AMTUL R. CARMICHAEL
Anticancer Research March 2014, 34 (3) 1147-1151;

Cardiotossicità da anticorpi monoclonali (trastuzumab)

Asymptomatic decrease in the left ventricular ejection fraction
(less commonly clinical heart failure)

- In the adjuvant setting, are appropriate to screen for cardiac dysfunction:
  - baseline assessment prior to starting trastuzumab
  - serial LVEF monitoring
    - at 3, 6, and 12 months after initiating trastuzumab
    - 18 months after initiating an anthracycline or other chemotherapy

- For patients with early breast cancer, cardiac assessments should be repeated:
  - every 3 months during treatment
    - and every 6 months following discontinuation of treatment until 24 months from the last administration
      - In patients who receive anthracycline-containing chemotherapy further monitoring: yearly up to 5 years from the last administration, or longer if a continuous decrease of LVEF is observed.

- In the metastatic setting, after a baseline assessment, LVEF is infrequently monitored in the absence of symptoms

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Cardiotossicità da anticorpi monoclonali (trastuzumab)

strongest risk factors:

- Previous or concurrent anthracycline
- Age greater than 50 years

Cardiotoxicity is reversible in many patients and responds to standard treatment for heart failure.

Many patients tolerate continued treatment or rechallenge with trastuzumab.

Trastuzumab can be safely administered with taxanes, radiation therapy, and endocrine therapy.

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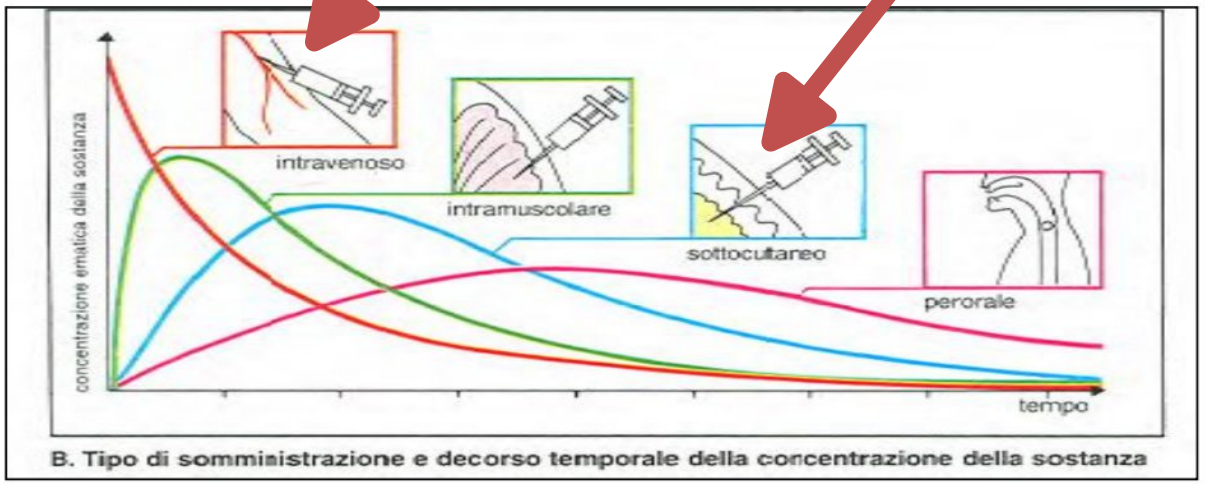
Cardiotossicità da anticorpi monoclonali (trastuzumab sottocute)

Important Missing Information	
Long term safety of Herceptin SC compared to Herceptin IV	
Evidence for linking the risk to the medicine	Patient treated with the Herceptin SC receive a higher cumulative dose of Herceptin compared to Herceptin IV. It is not yet known whether this higher cumulative dose may lead to more adverse effects which can only be observed after a longer follow-up.
Risk factors and risk groups	As above
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 Undesirable effects (Subcutaneous vi…) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk min… Information:** **Pack size:** Eac… Legal Status: H… Additional risk … measures
Additional pharmacovigilance activities	Additional phar… None

..higher cumulative dose!

Follow up!



B. Tipo di somministrazione e decorso temporale della concentrazione della sostanza

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Cardiotossicità da anticorpi monoclonali

(altri agenti biologici HER2-target)

Risk of ***cardiotoxicity seems to be less*** with ado-trastuzumab emtansine (T-DM1), and pertuzumab.

- A baseline assessment of LVEF is appropriate.
- As with trastuzumab, in the metastatic setting, LVEF is infrequently monitored during therapy in the absence of symptoms.

- dose adjustment in patients who develop cardiotoxicity during therapy with these agents.

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Cardiotossicità da anticorpi monoclonali (biologici)

Rituximab

- ***Arrhythmias and angina have been reported during less than 1 percent of infusions,***
- ***Acute infusion-related deaths have been seen in less than 0.1 percent.***

These deaths appear to be related to an **infusion-related complex of hypoxia, pulmonary infiltrates, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.**
Long-term cardiac toxicity has not been reported with rituximab administration.

Alemtuzumab

is associated with ***a significant risk of heart failure and/or arrhythmias.***

- The mechanism of this toxicity is not known,
- Partial or total resolution of symptoms after discontinuing treatment.

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Cardiotossicità da anticorpi monoclonali (checkpoint inhibitor immunotherapy ICI)

Cardiotoxicity may develop in the absence of a history of significant cardiac risk factors.
AEs include ***myocarditis, pericarditis, heart failure, arrythmias, and vasculitis***.

Venous thromboembolism may also be seen, although its relationship to checkpoint inhibitor immunotherapy is less clear.

The time to onset was variable, but fatal myocarditis has been reported after a single treatment with the combination of nivolumab plus ipilimumab.
Observational studies also suggest that the incidence of myocarditis is higher in patients treated with the combination immunotherapy compared with single-agent immunotherapy.

High-dose steroids have been used to treat cardiac complications….

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Agenti biologici, Immunocheckpoint inibitori

- HER2: inhibition cell survival pathways

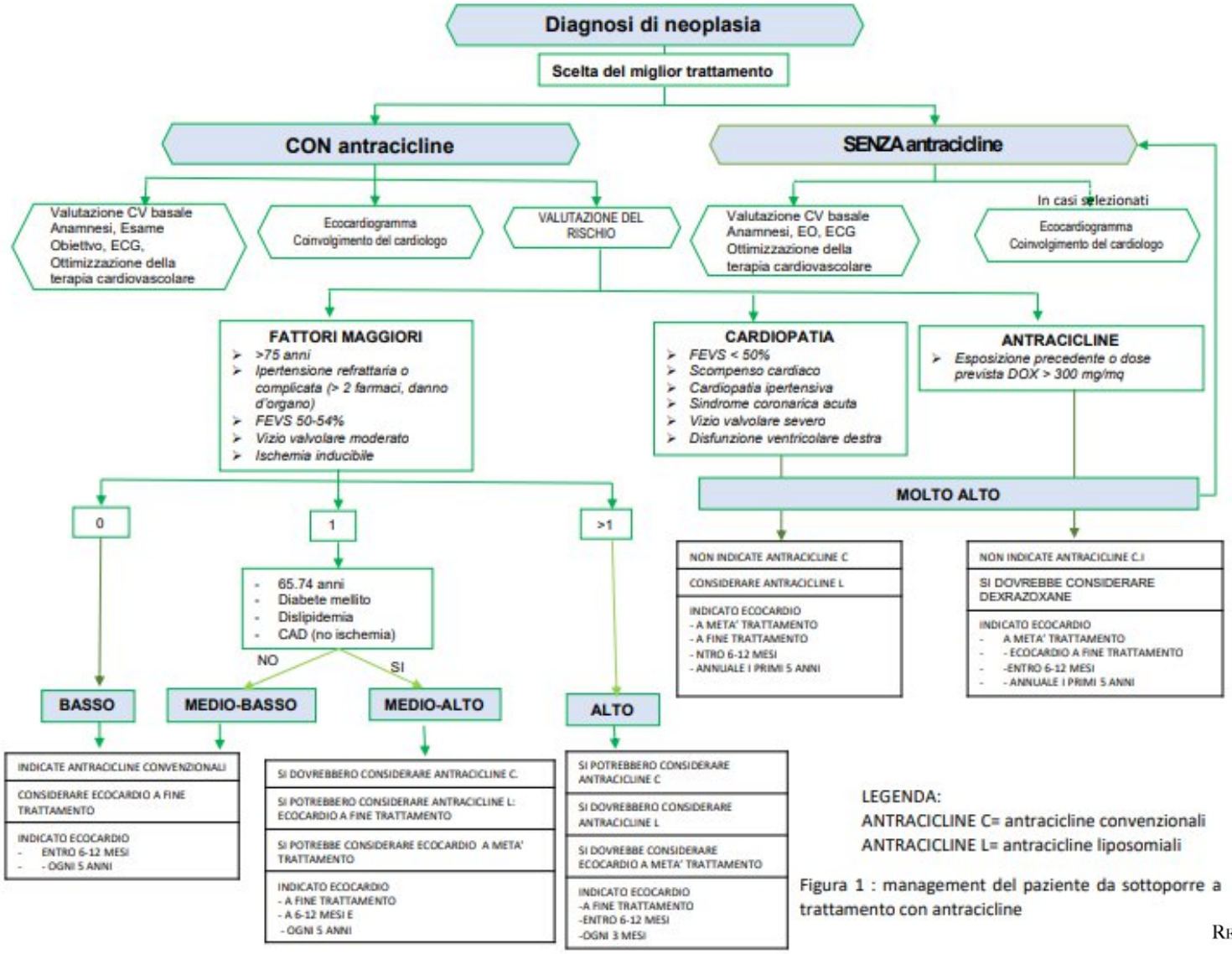
- ICI agents may result in T cells target ligands on cardiac myocytes
- ICI T-cell invasion and myocarditis.

- Cardiac hypersensitivity refers to an inflammatory response that:
  - is not dose-dependent,
  - may arise at any time during treatment,
  - even with minimal drug concentrations,
  - is accompanied by anti-drug antibodies (IgG).

Trends in Cardiovascular Medicine
21/09/2022

Oncoimmunology. 2014; 3: e27987.

Monitoraggio della funzione miocardica, in paziente sottoposto a trattamento antineoplastico.



LEGENDA:
ANTRACICLINE C= antracicline convenzionali
ANTRACICLINE L= antracicline liposomiali

Figura 1 : management del paziente da sottoporre a trattamento con antracicline

PLACE 9ª Edizione

Circuito "virtuoso" da alimentare

Ricerca pre-marketing

Ricerca post-marketing

Monitoraggio uso, farmacovigilanza

Disponibilità in clinica con buon rapporto rischio/beneficio

Standard terapeutici e linee guida che valutano rischio/beneficio (formulare raccomandazioni)

MENU AIFA Agenzia Italiana del Farmaco

home > Sicurezza dei farmaci > La Rete Nazionale di Farmacovigilanza (RNF)

La Rete Nazionale di Farmacovigilanza (RNF)

Il sistema italiano di farmacovigilanza si basa sulla Rete Nazionale di Farmacovigilanza (RNF) che garantisce la raccolta, la gestione e l'analisi delle segnalazioni di sospette reazioni avverse a farmaci (ADR).

Alla RNF possono accedere solo gli utenti registrati al **Portale dei Servizi di AIFA**, in possesso di username e password, di un'identità digitale SPID, di una Carta Nazionale dei Servizi (CNS) o di una Carta di Identità Elettronica (CIE), e che appartengono alle seguenti strutture: **Agenzia Italiana del Farmaco**, **Ministero della Salute**, **Istituto Superiore di Sanità**, **Regioni**, **Centri Regionali di Farmacovigilanza**, **Strutture Sanitarie** - Aziende Sanitarie Locali (ASL), Aziende Ospedaliere (AO) e Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) - **Forze Armate** e **Aziende farmaceutiche** (queste ultime con visibilità di dati limitata alle strutture sanitarie).

Modalità di registrazione degli utenti

Per ogni singola struttura o azienda farmaceutica, oltre alla nomina del **Responsabile Locale di Farmacovigilanza (RLFV)** o **Responsabile di Farmacovigilanza per l'Azienda farmaceutica**, potrà essere designata anche la figura del **Deputy** per supportare il Responsabile nella gestione delle segnalazioni di reazioni avverse e/o farne le sue veci in caso di assenza temporanea. Gli utenti designati a ricoprire il ruolo di Responsabile o Deputy devono

Grazie per l'attenzione

IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA
ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO