I percorsi appropriati assistenziali e terapeutici in prevenzione secondaria *approccio al paziente ad alto rischio cardiovascolare*

FAD sincrona

10 giugno 2022

«cosa chiede l'ematologo al cardiologo»

Dott.ssa Laura Cudillo

AO S.Giovanni-Addolorata

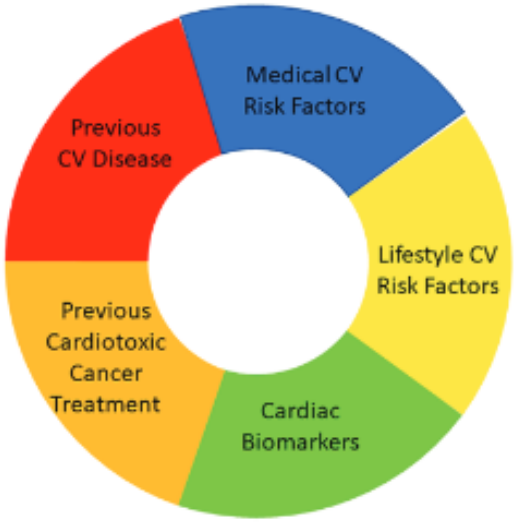
SOMMARIO

- Gestione dei pazienti
- Farmaci
- Danno
- Cardio-oncologia in Ematologia

ESC European Society of Cardiology
European Journal of Heart Failure (2020) 22, 1945–1960
doi:10.1002/ejhf.1920
POSITION PAPER

Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society

Età
valutazione geriatica



Baseline CV Risk Assessment Checklist

Cardiac history
Cancer treatment history
CV risk factors

Blood pressure
HbA1c
Cholesterol profile

*Cardiac troponin**
*BNP or NT-proBNP**

ECG

Echocardiogram

Figure 2 The different risk factors which contribute to baseline cardiovascular (CV) risk in a cancer patient scheduled to receive a cardiotoxic cancer treatment, and a checklist of the clinical history and investigations required at baseline prior to starting a cardiotoxic cancer therapy. *Cardiac biomarkers (troponin and natriuretic peptides) should be measured where available. BNP, brain natriuretic peptide; ECG, electrocardiogram; HbA1c, glycated haemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide.

FARMACI

- L’efficacia della chemioterapia è “tempo sensibile”
  - Mantenere la periodicità
  - Ritardo o interruzione influenzano negativamente la risposta e l’outcome del paziente
- Come ridurre la cardiotossicità preservando efficacia?
- Chemioterapici convenzionali: ciclofosfamide, antracicline, 5FU ecc…
- Armamentario terapeutico in continua espansione
  - nuove molecole
  - terapie immunologiche

ciclofosfamide

Agente alchilante

Polichemioterapie per malattie linfoproliferative: CHOP, CVP CHOEP ecc…

Regimi di condizionamento nel trapianto di cellule staminali emopoietiche

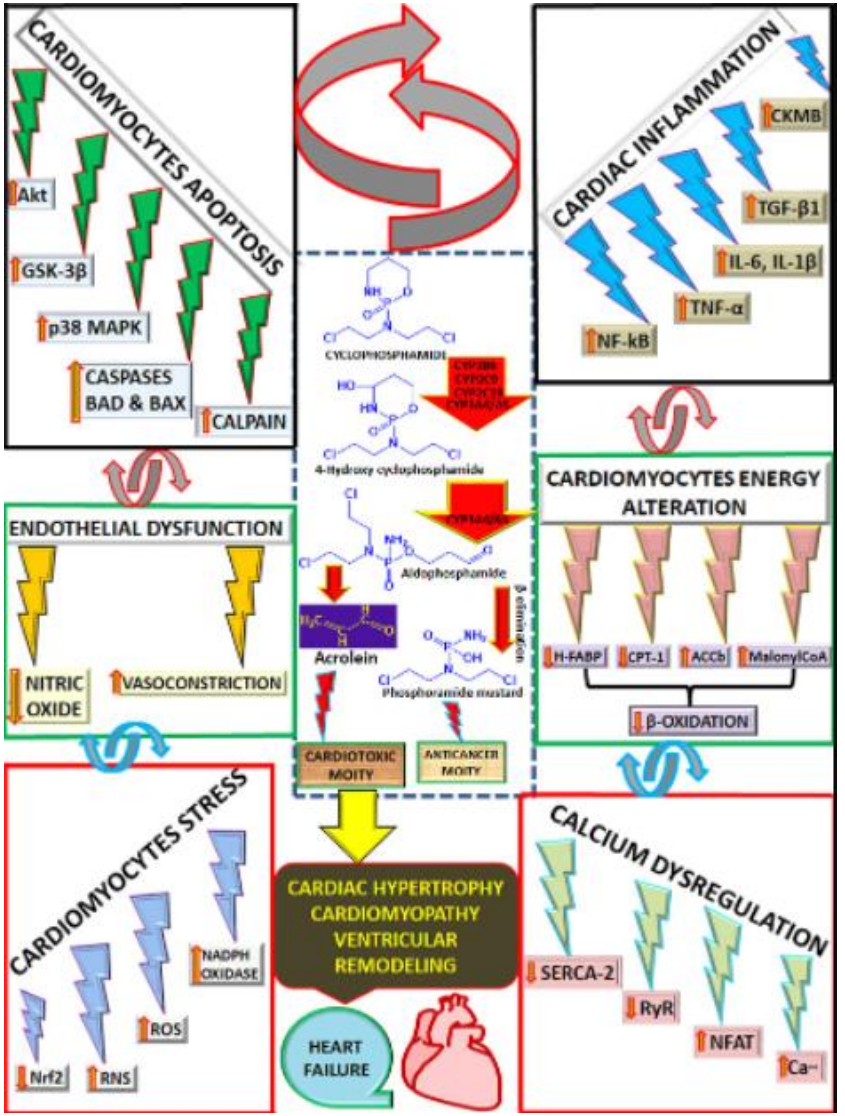
Cardiotossicità 7-28%

Mortalità 11-43%

Dose tossica 170-1180 mg/kg

Metabolita acroleina tossica per miocardio e cellule endoteliali

Prevenzione: dose, eliminazione acroleina, antiossidanti



Iqubal A et al Life Sci 2019 218:112-131

antracicline

- adriamicina, daunoblastina, epirubicina
- Inserite in cicli di polichemioterapia: linfomi, leucemia mieloide acuta, leucemia linfatica acuta, mieloma
- Linfoma diffuso a grandi cellule B: **R-CHOP** rituximab, ciclofosfamide, adriamicina, vincristina, prednisone
  - I linea di terapia
  - gold standard remissioni complete 60%
- Tossicità cardiaca dose-dipendente meccanismi:
  - danno mitocondriale, alterato metabolismo del ferro, apoptosi, danno DNA
  - acuta e cronica
- Screening dei pazienti pre-terapia e in follow up
- Pazienti unfit:
  - riduzione dose (mini CHOP), farmaci alternativi gemcitabina, etoposide, adriamicina liposomiale, agenti cardioprotettivi (?)

ORIGINAL RESEARCH ARTICLE

Nonpegylated liposomal doxorubicin combination regimen in patients with diffuse large B-cell lymphoma and cardiac comorbidity. Results of the HEART01 phase II trial conducted by the Fondazione Italiana Linfomi

S Luminari et al Hematological Oncology, 2017

Obbiettivo primario attività e efficacia della doxorubicina liposomiale

ciclo R-COMP

50 PTS 76 anni età mediana

Valutazioni cardiologiche dopo 3 mesi, fine terapia, ogni 3 mesi per 2 anni

- Comorbidità cardiaca :cardiopatia ischemica 35% fibrillazione atriale 15% ipertrofia ventricolare 13% LVEF <50% 12%
- Remissione completa 56%
- Remissione parziale 16%
- OS a 3 anni 50% no decessi per eventi cardiaci

TABLE 4 Summary of cardiac events during treatment

	Population (N = 50)	
Cardiac disorder	Grades 1-2, n (%)	Grades 3-4, n (%)
Heart failure	1(2)	1(2)
LVEF drop ≥20%	2(4)[a]	3(6)
Increased troponin	2(4)	-
Angina	-	1(2)
Atrial fibrillation	-	1(2)
Tot	**5(10)**	**6(12)**

Abbreviations: LVEF, left ventricular ejection fraction.

[a]Asymptomatic.

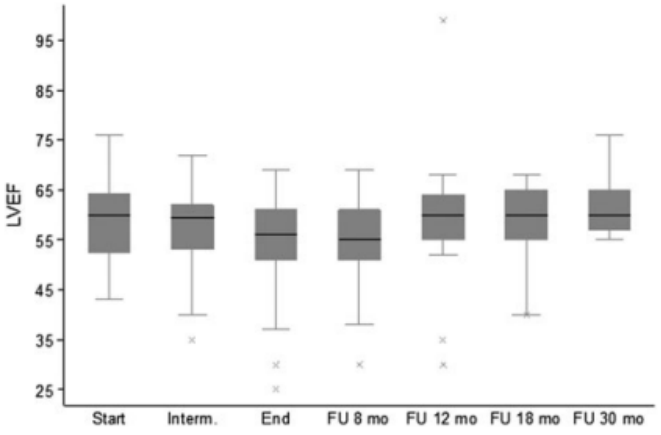


FIGURE 2 Left ventricular ejection fraction trend from baseline to end of follow up

R-COMP versus R-CHOP as first-line therapy for diffuse large B-cell lymphoma in patients ≥60 years: Results of a randomized phase 2 study from the Spanish GELTAMO group

Sancho JM et al Cancer Medicine. 2021;10:1314–1326

Razionale daunorubicina liposomiale associata minore cardiotossicità

Obbiettivo primario cardiotossicità subclinica: riduzione <55% LVEF termine del trattamento

Obbiettivo secondario : sicurezza, efficacia; valutazione troponina e proBNP e LVEF nel follow up

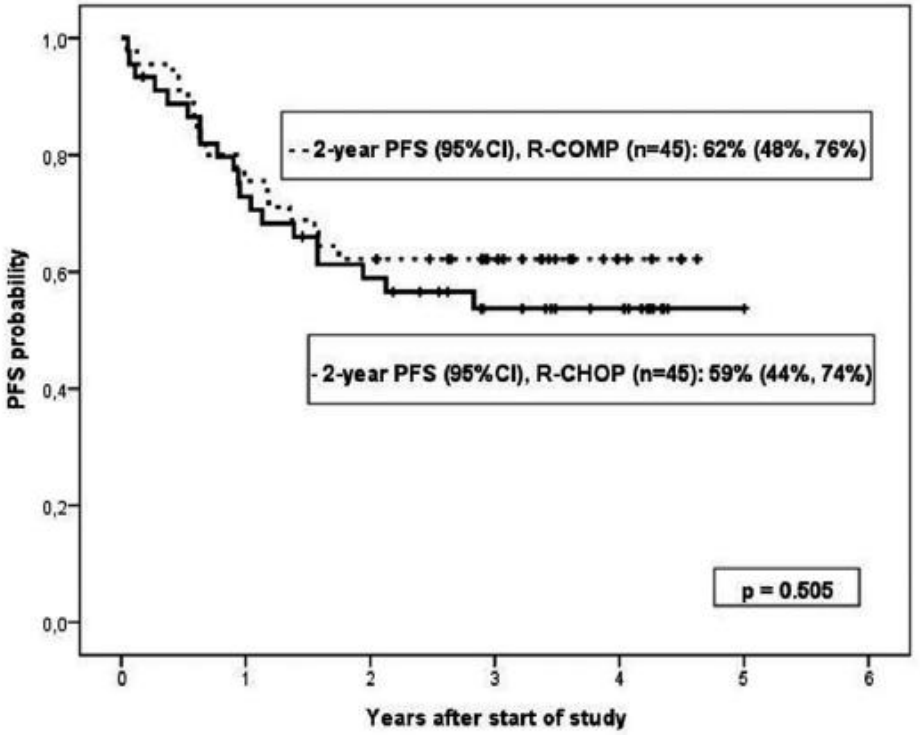
Arruolati 90 pazienti 45 per braccio

Risultati

- no differenze in LVEF al termine della terapia
- Troponina aumentata al VI ciclo nel braccio R-COMP v/s R-CHOP: 0% vs. 63%, p = 0.001
- Efficacia simile

TABLE 5 Cardiovascular adverse events in the R-CHOP and R-COMP arms

Adverse event	R-CHOP (n = 45)	R-COMP (n = 45)
Atrial fibrillation	3[a]	1
Tachycardia	3	1
Bradycardia/tachycardia	0	1
Heart failure	2[b]	1
Myocardial infarction	1[c]	0
Atrioventricular block	0	1
Overall cardiovascular events	9	5



Circulation Research

REVIEW

Mechanisms of Cardiovascular Toxicities Associated With Immunotherapies

Alan H. Baik, Olalekan O. Oluwole, Douglas B. Johnson, Nina Shah, Joe-Elie Salem, Katy K. Tsai, Javid J. Moslehi

Immunoterapici e farmaci target:

- Check point inhibitors
- CAR T Cell chimeric antigen receptor T cell
- Anticorpi bispecifici (blinatumomab)
- Anticorpi monoclonali
- Inibitori di tirosinchinasi

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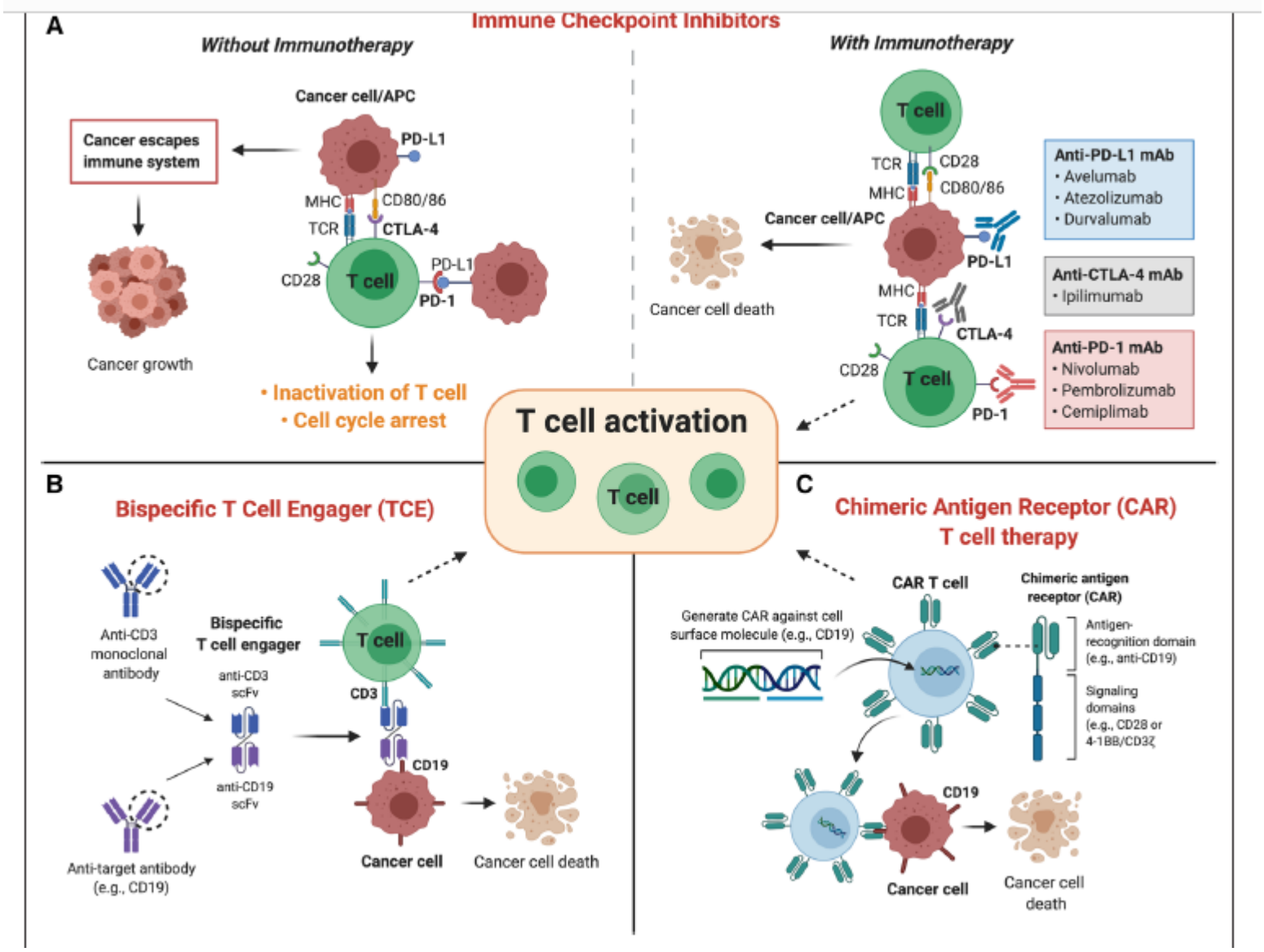

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Table 1. Types of Immunotherapy

Immunotherapy	Examples	Mechanism of action	Cancer targets
CAR T-cell therapy	Axicabtagene ciloleucel (Yescarta)	Adoptive cell transfer	Relapsed or refractory (r/r) non-Hodgkin lymphoma (DLBCL), primary mediastinal B cell lymphoma, high grade B cell lymphoma, transformed follicular lymphoma
	Tisagenlecleucel (Kymriah)	T cell–mediated killing of cancer cells	
	Brexucabtagene autoleucel (Tecartus)		r/r DLBCL
			r/r mantle cell lymphoma
Bispecific antibodies	Blinatumomab (Blincyto)	CD3 and CD19-targeting bispecific antibody	Relapsed or refractory B-cell precursor ALL
	AMG 420	CD3 and BCMA	Multiple myeloma
	IMCgp100 (Tebentafusp)	CD3 and GP100	Metastatic uveal melanoma
	AFM13	CD16A and CD30	CD30-positive Hodgkin's lymphoma
	MGD006 (Flotetuzumab)	CD3 and CD123	Acute myeloid leukemia
Immune checkpoint inhibitors	See Table 2	Block checkpoint proteins from interacting with partner proteins, allowing T cell-mediated killing of cancer cells	See Table 2
Monoclonal antibody therapy*	Alemtuzumab (Lemtrada)	Monoclonal antibody, binds to CD52 (protein on surface of mature lymphocytes); CD52-bearing lymphocytes targeted for destruction	Chronic lymphocytic leukemia
	Rituximab (Rituxan)	Chimeric monoclonal antibody targets CD20 (primarily found on surface of immune B cells); promotes B cell elimination	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, GPA and MPA
	Elotuzumab (Empliciti)	SLAMF7 (CD319)-directed immunostimulatory antibody	Relapsed multiple myeloma
	Daratumumab (Darzalex)	Anti-CD38, promotes apoptosis	Multiple myeloma, diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma
Cytokines†	High-dose IL-2	Promotes expansion of NK and T lymphocytes	Advanced RCC, metastatic melanoma
	Recombinant interferon-α	Potent antiangiogenic activity[152]	Hairy cell leukemia
			Follicular non-Hodgkin lymphoma
			Melanoma
			AIDS-related Kaposi's sarcoma
			CML

Anticorpi monoclonali bi-specifici

- differenti siti di legame:
- anti CD3 linfocita + anti antigene cellula neoplastica :
  - Blinatumomab antiCD19: Leucemia linfatica B
  - Tossicità cardio vascolare precoce/moderata:
  - Ipertensione, ipotensione, tachicardia sinusale
  - glofitamab mosunetuzumab anti CD20 2 siti legame: LNH

REVIEW

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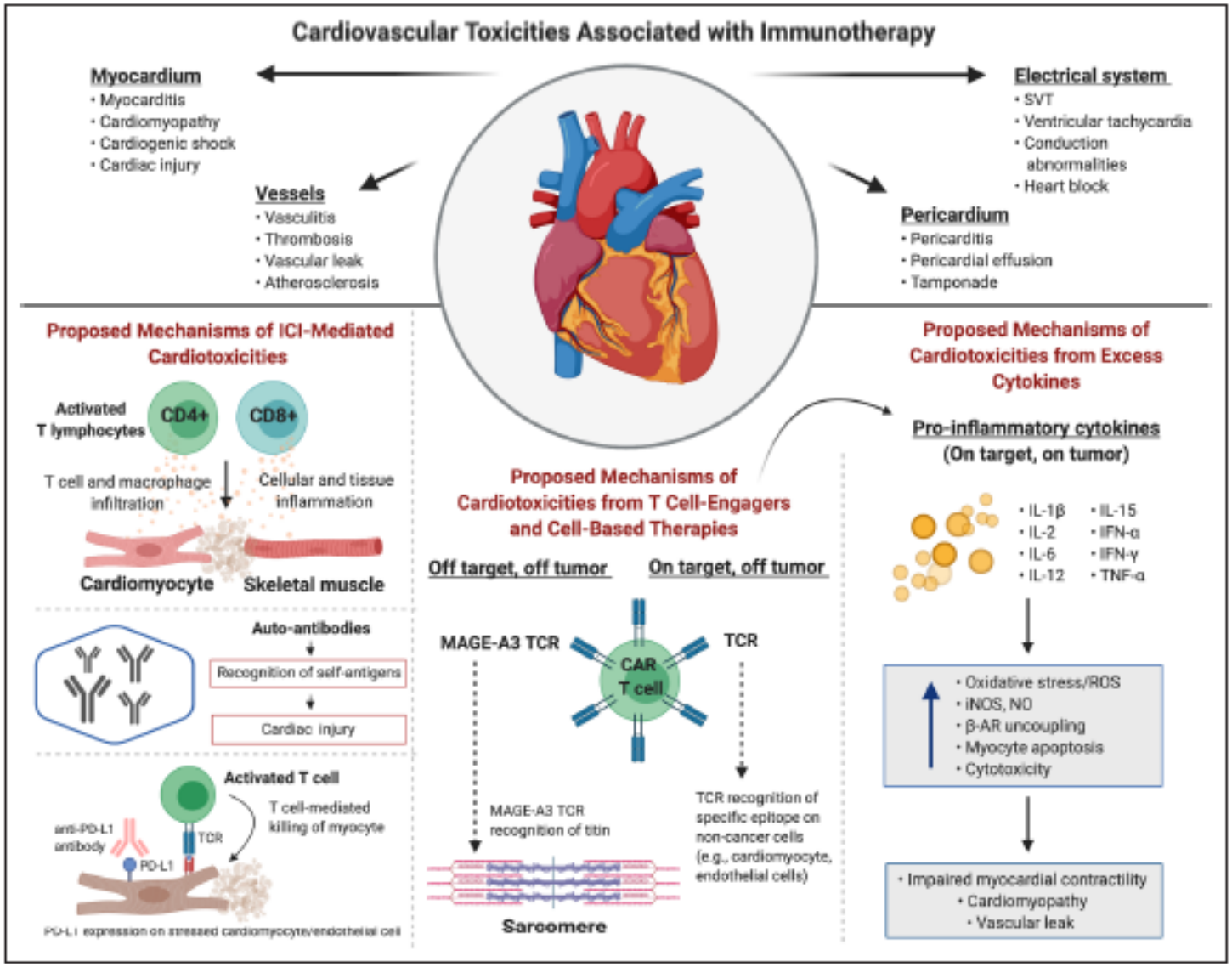


Figure 2. Proposed mechanisms of cardiovascular toxicities associated with immunotherapies.

CAR T Cell Chimeric Antigen Receptor T cell

linfociti CD3 geneticamente modificati ex-vivo

Infettati con un retrovirus che codifica per recettore dei linfociti T (TCR) specifico per un dato antigene della cellula neoplastica + molecole co-stimolatorie attivanti il linfocita T

Il linfocita ingegnerizzato produce il recettore chimerico

Anti CD19: linfomi e leucemia linfoblastica

Anti BCMA: mielomi

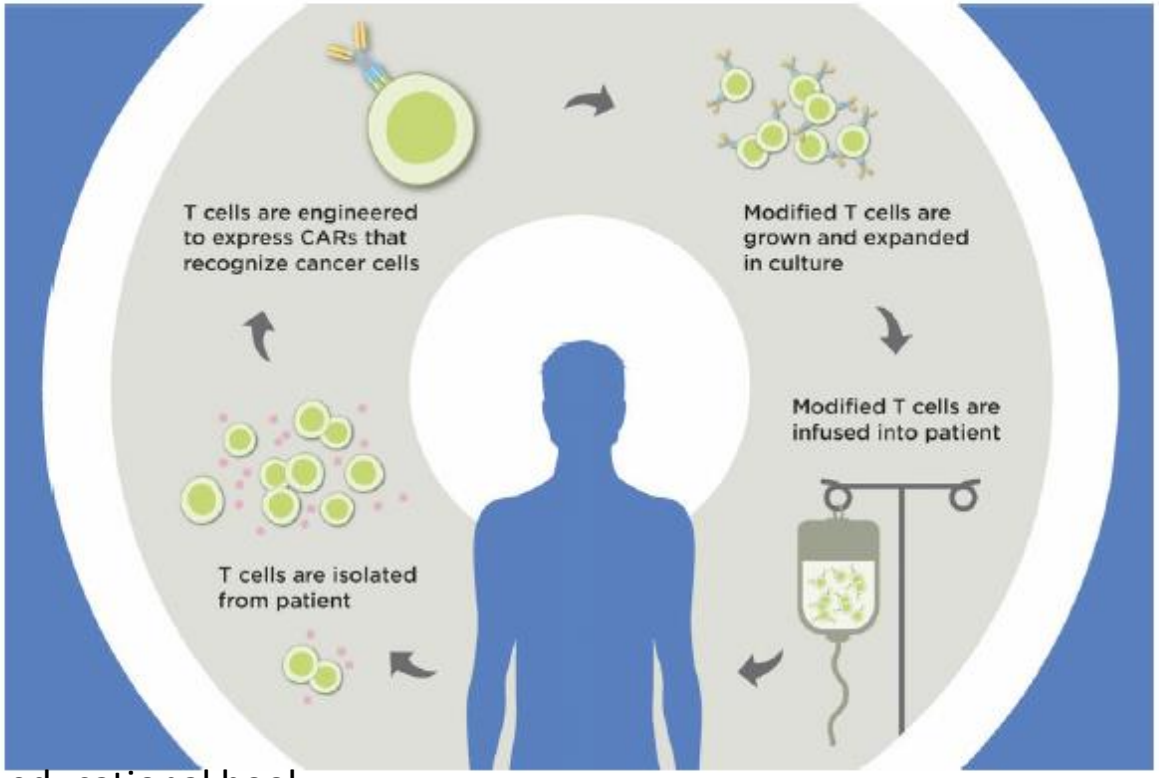


FIGURE 2. Process for Collection and Administration of CAR T Cells

Abbreviation: CAR, chimeric antigen receptor.

Santomasso B et al ASCO 2019 educational book

Circulation Research

REVIEW

Mechanisms of Cardiovascular Toxicities Associated With Immunotherapies

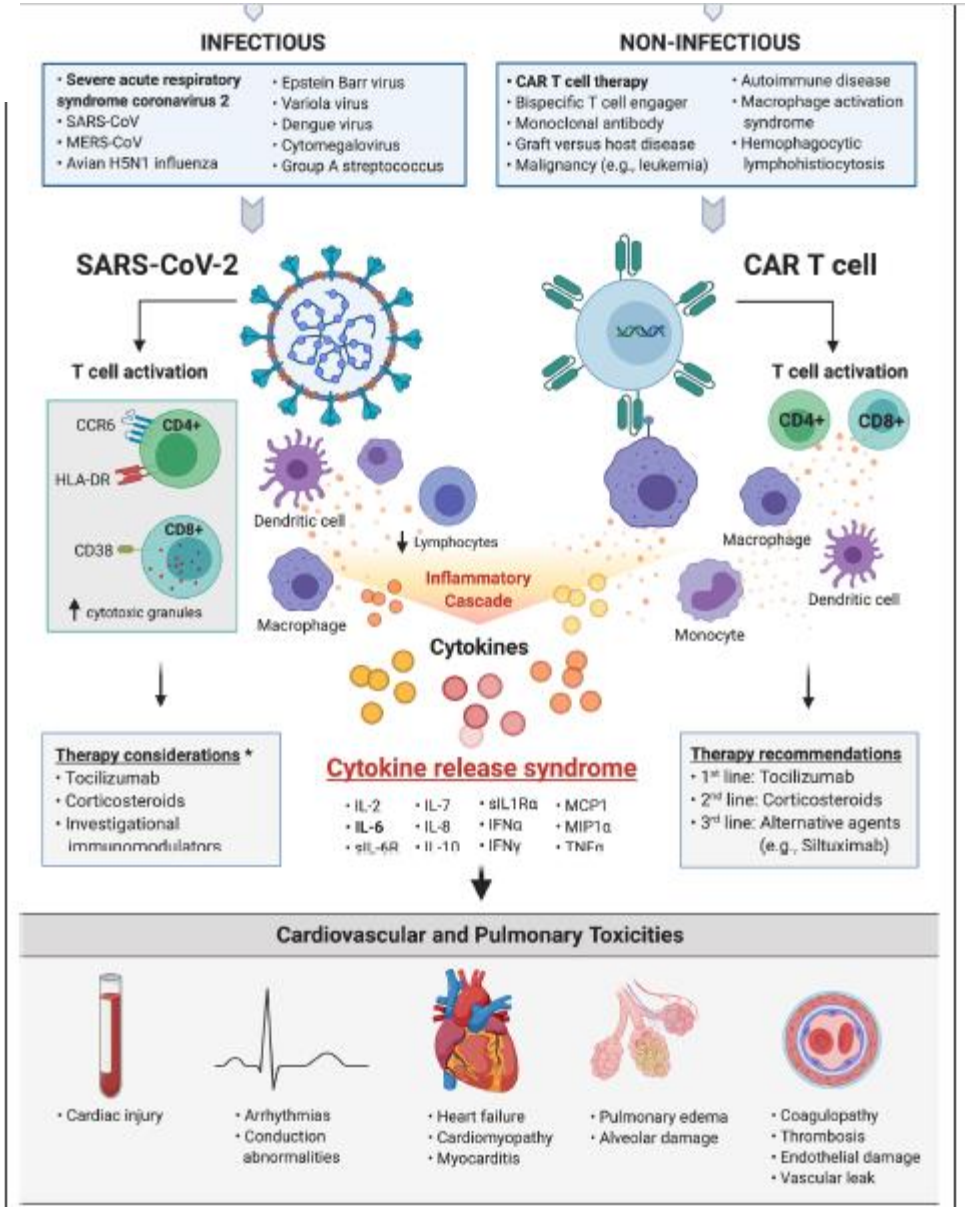
Alan H. Baik, Olalekan O. Oluwole, Douglas B. Johnson, Nina Shah, Joe-Elie Salem, Katy K. Tsai, Javid J. Moslehi

Sindrome iperinfiammatoria da rilascio di citochine CRS:

Cytokine

Release

Syndrome



Citation: Molecular Therapy — Oncolytics (2016) 3, 16011; doi:10.1038/mto.2016.11
Official journal of the American Society of Gene & Cell Therapy

www.nature.com/mto

REVIEW

Toxicity and management in CAR T-cell therapy

Challice L Bonifant[1], Hollie J Jackson[2], Renier J Brentjens[2] and Kevin J Curran[3]

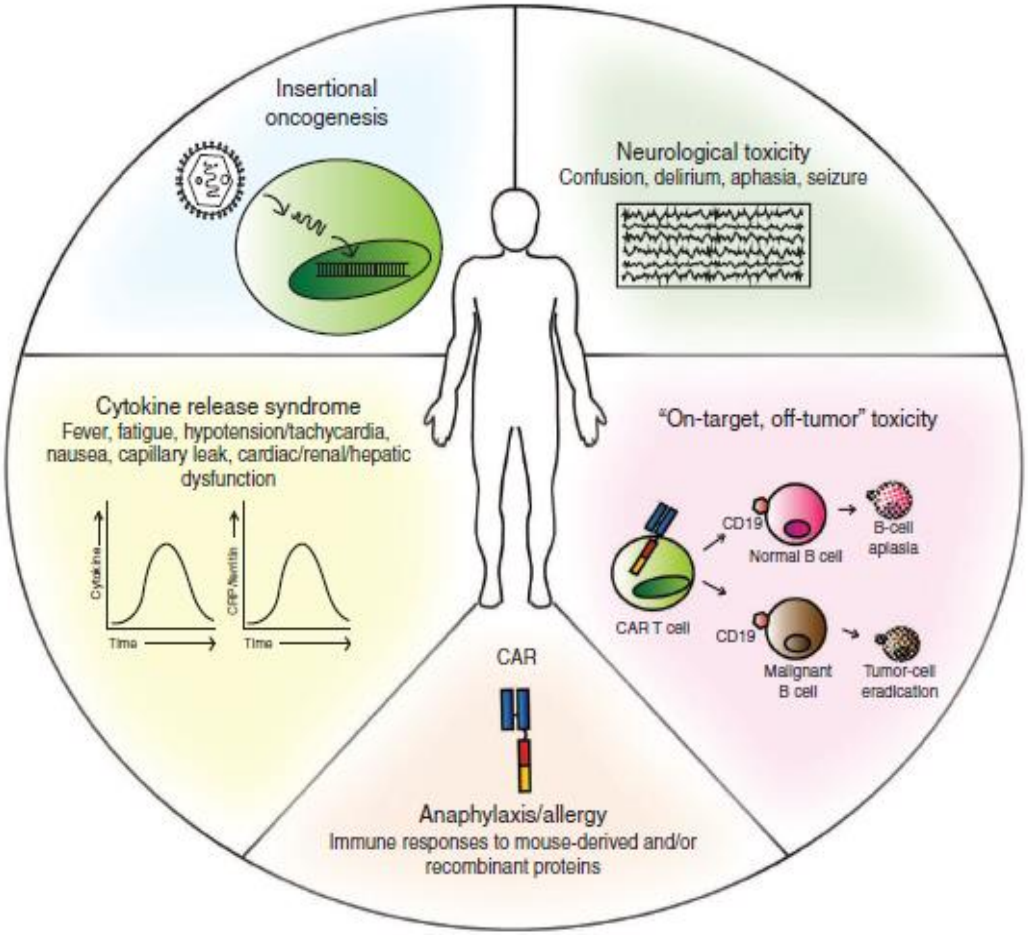


Figure 1 Toxicities of chimeric antigen receptor (CAR) T-cell therapy. Depiction of reported/potential toxicities following the use of CAR T cells: insertional oncogenesis (theoretical); neurological toxicity; "on-target, off-tumor" toxicity (engagement of target antigen on nonpathogenic tissues); anaphylaxis/allergy (host reaction to foreign antigen expressed by the CAR T cell); cytokine release syndrome (systemic inflammatory response following activation of CAR T cells). CRP, C-reactive protein.

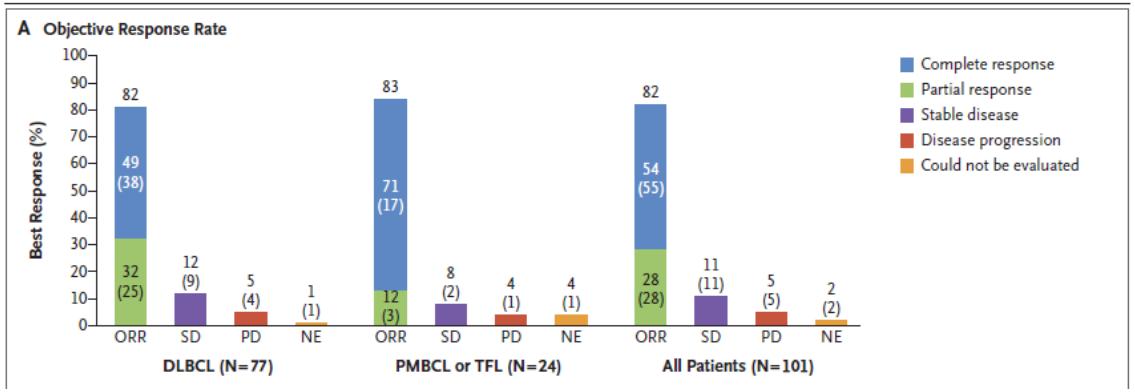
ORIGINAL ARTICLE

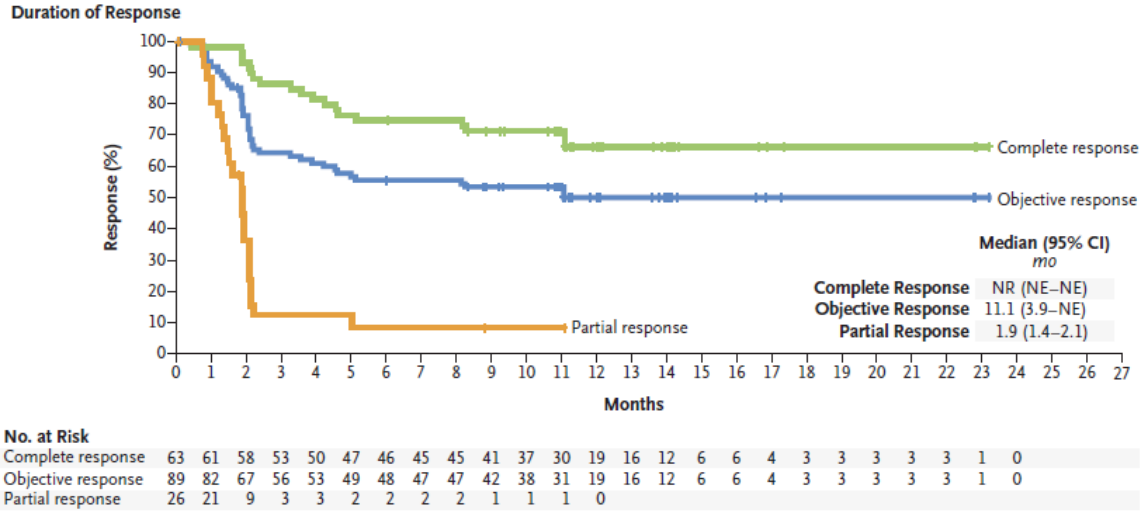
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

Neelapu SS NEJM 2017,377,2513

Table 1. (Continued.)

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Refractory subgroup at study entry — no. (%)			
Primary refractory	2 (3)	0	2 (2)
Refractory to second-line or subsequent therapy	59 (77)	19 (79)	78 (77)
Relapse after autologous stem-cell transplantation	16 (21)	5 (21)	21 (21)





Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial
Frederick L Locke et al
Lancet Oncol. 2019 January ; 20(1): 31–42

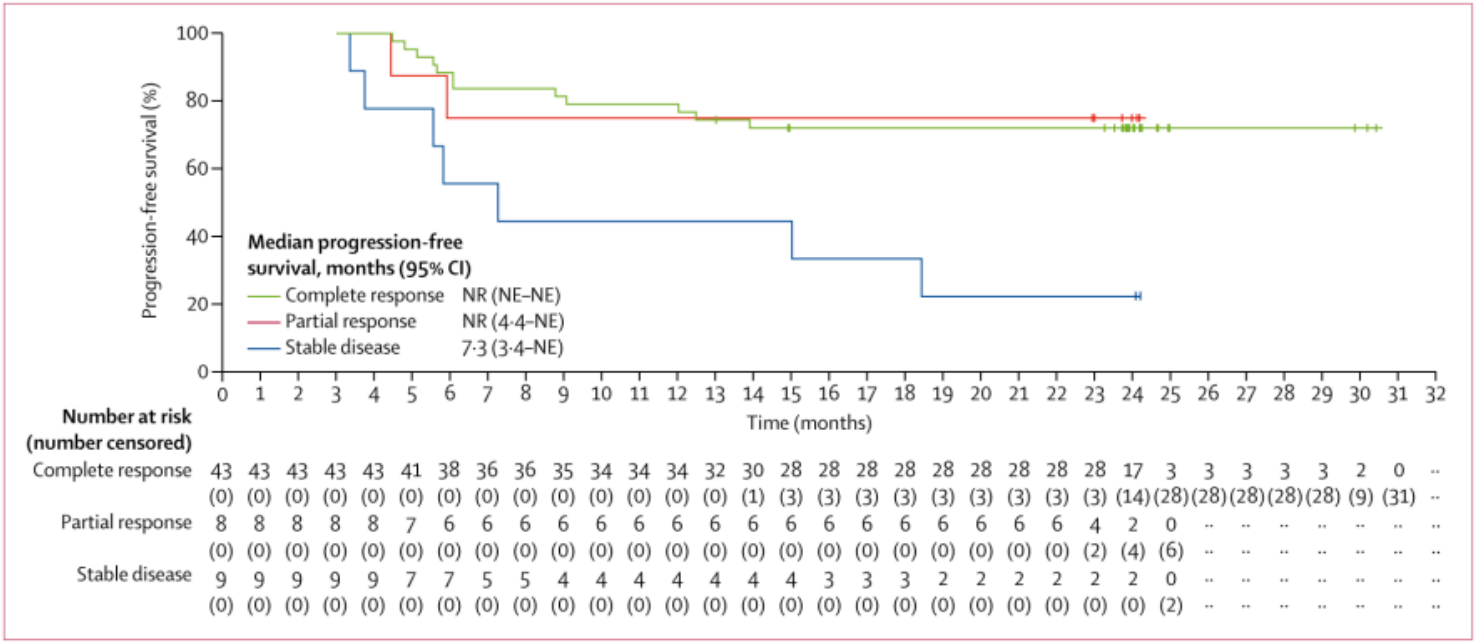


Figure 2: Post-hoc analysis of investigator-assessed progression-free survival by response status at 3 months after axicabtagene ciloleucel

60 patients with ongoing complete response, partial response, or stable disease month 3 in phase 2 are shown. The x-axis shows time since infusion of chimeric antigen receptor T cells. Four of eight patients with partial responses and four of nine patients with stable disease at 3 months subsequently converted to complete responses. NR=not reached.

International Journal of
Molecular Sciences

MDPI

Review

Cardiotoxicity Induced by Protein Kinase Inhibitors in Patients with Cancer

Aleksandra Grela-Wojewoda [1,*], Renata Pacholczak-Madej [1,2], Agnieszka Adamczyk [3], Michał Korman [4] and Mirosława Püsküllüoğlu [1]

- Inibitori di kinasi gruppo eterogeneo di molecole dirette contro enzima kinasi bloccano la fosforilazione e la proliferazione cellulare
- monoterapia o in associazione con altri farmaci

In EMATOLOGIA sono utilizzati inibitori di:

1. Tirosin kinasi di Bruton: ibrutinib, acalabrutinb → linfoma mantellare, LLC, macroglobulinemia di Waldestrom
- Tossicità ipertensione (2-80%), FA (13%) aritmie ventricolari (1%), IMA (14%)
2. Janus kinasi JAK : ruxolitinib → mielofibrosi policitemia vera
- Tossicità ipertensione (>10%)
3. BCR/ABL: imatinib, dasatinib, nilotinib, bosutinib, ponatinib → LMC, LLA Ph positiva
- Tossicità cardiomiopatia, allungamento QTc, ritenzione idrica

REVIEW article
Front. Cardiovasc. Med., 19 November 2021 | https://doi.org/10.3389/fcvm.2021.758010

Tyrosine Kinase Inhibitors-Induced Arrhythmias: From Molecular Mechanisms, Pharmacokinetics to Therapeutic Strategies

Mengfei Cheng[1†], Fang Yang[2†], Jiahui Liu[1†], Dan Yang[3], Shuo Zhang[1], Yang Yu[1], Shuai Jiang[1*] and Mei Dong[1*]

[1]Department of Pharmacy, Harbin Medical University Cancer Hospital, Harbin, China
[2]The First Department of Respiratory Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China
[3]Department of Clinical Laboratory, Harbin Medical University Cancer Hospital, Harbin, China

Name	Vandetanib	Ibrutinib	Ponatinib	Nilotinib	Dasatinib
Target	VEGFR-2; EGFR; RET	BTK; MAPK; PI3K	BCR-ABL; PDGFR; c-KIT; VEGFR; EGFR	BCR-ABL; PDGFR-α/β; c-kit; DDR	BCR-ABL; c-KIT; SFKS; PDGFR-α/β
Effect on QT interval	Prolong QT interval and with a positive drug exposure-dependent risk	Shorten QT interval	Prolong QT interval, no correlation was found between drug exposure and QT prolongation	Prolong QT interval with a positive correlation between exposure and risk	Rarely causes QT interval prolongation
Effect on AF	With a low incidence from 0.43 to 1.79%	Highest incidence of AF, nearly 10–15%	With a low incidence, about 1.29%	With a high incidence followed by ibrutinib	Rarely causes AF
Metabolized by	CYP3A4	CYP3A4	CYP3A4/5, CYP2C6, CYP2C8	CYP3A4	CYP3A4, CYP2C8

American Heart Association | American Stroke Association.

Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review

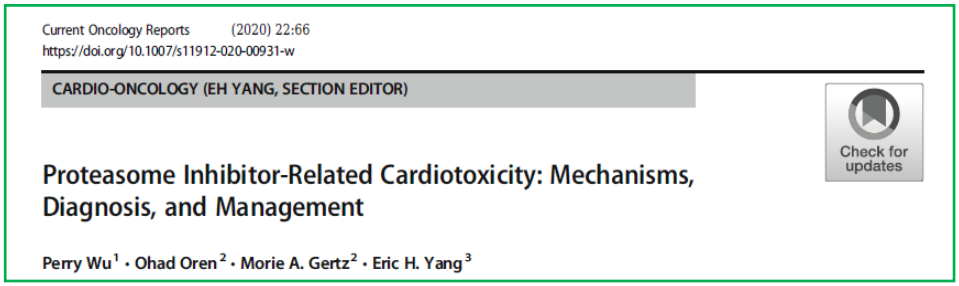
Andreu Porta-Sánchez, MD MSc; Cameron Gilbert, MD; Danna Spears, MD; Eitan Amir, MD, PhD; Joyce Chan, PharmD, MSc; Kumaraswamy Nanthakumar, MD; Paaladinesh Thavendiranathan, MD, SM

ALLUNGAMENTO QTc

- Monitoraggio costante durante il trattamento
- Misura QTc fondamentale per:
  - Ridurre rischi complicanze
  - Modulare dose
  - Evitare stop inutili della chemioterapia
  - Range incidenza 0-22%
  - QTc >500 più comune in terapie target (TKI) e triossido di arsenico
    - rischio torsione di punta

→ uso concomitante farmaci
inibitori CYP3A4
insufficienza renale e epatica
elettroliti

High risk (>10% incidence)	Arsenic trioxide Bosutinib Capecitabine Cediranib Combretastatin (CA4P) Enzastaurin Vadimezan Vorinostat
Moderate risk (5%–10% incidence)	Belinostat Dasatinib Dovitinib Lenvatinib Sorafenib Sunitinib Vandetanib
Low risk (1%–5% incidence)	Aflibercept Imatinib Lapatinib Nilotinib Nintedanib Paclitaxel Panobinostat Ponatinib Romidepsin Vemurafenib
Very low risk (<1% incidence)	Anthracyclines Fluorouracil Afatinib Ceritinib Crizotinib Fludarabine Pazopanib Pertuzumab Trastuzumab



Current Oncology Reports (2020) 22:66
https://doi.org/10.1007/s11912-020-00931-w

CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Check for updates

Proteasome Inhibitor-Related Cardiotoxicity: Mechanisms, Diagnosis, and Management

Perry Wu[1] · Ohad Oren[2] · Morie A. Gertz[2] · Eric H. Yang[3]

Inibitori del proteasoma mieloma, linfomi:

- **Carfilzomib inibizione irreversibile**
- Bortezomib
- Ixazomib

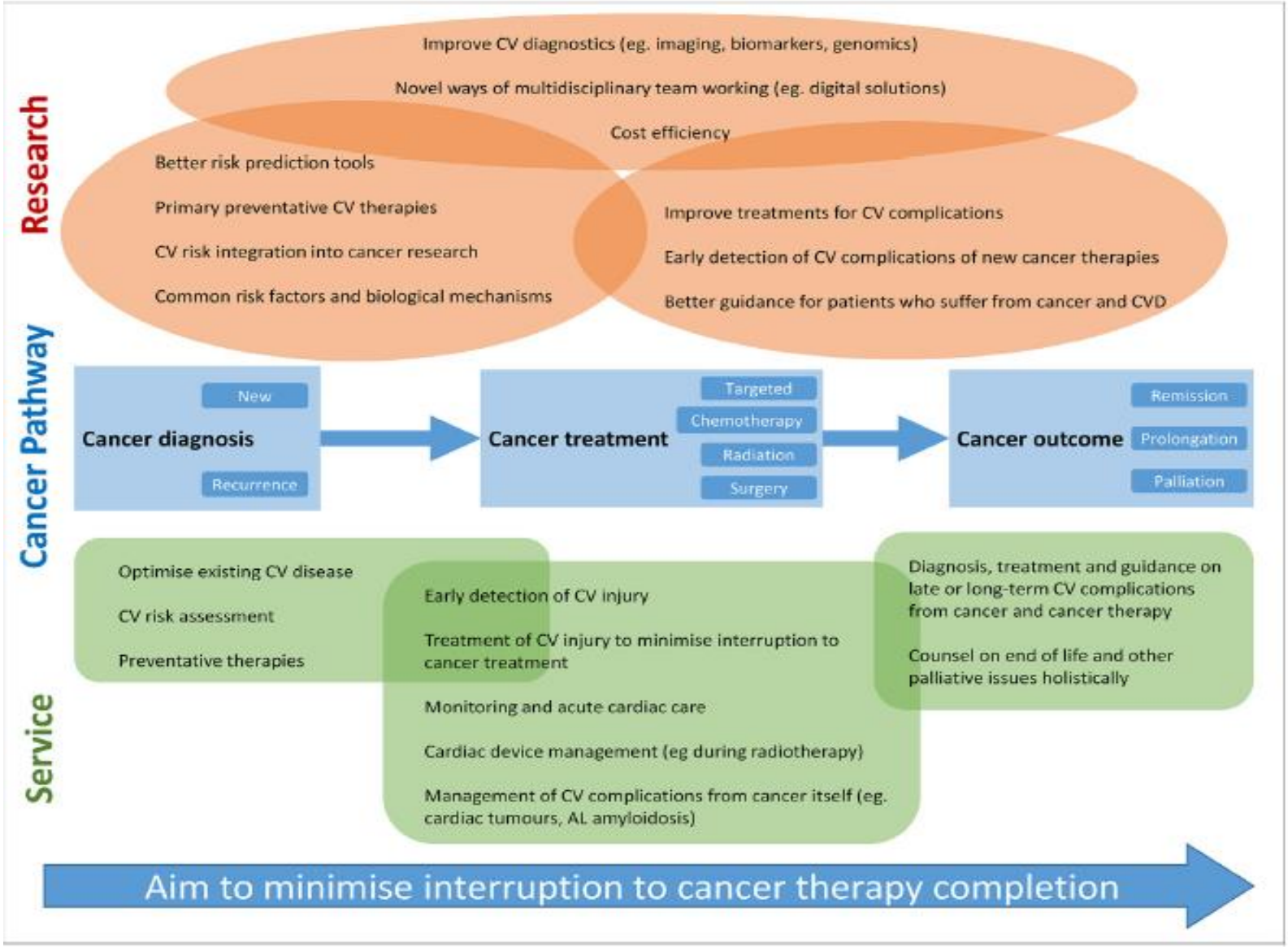
Meccanismo antitumore:

1. Inibizione proteasoma
2. Accumulo aggregati proteici nel reticolo endoplasmico
3. Attività antiproliferativa induzione apoptosi cellulare

Studi preclinici hanno dimostrato elevata sensibilità delle cellule miocardiche a inibizione del proteasoma

- **Tossicità cardiovascolare**
  - precoce
  - Ipertensione
  - Aritmia
  - Insufficienza cardiaca
  - Ischemia
  - Trombo-embolia
  - Morte improvvisa
- **Valutazione preterapia**

cosa chiede l'ematologo al cardiologo



GRAZIE PER L'ATTENZIONE