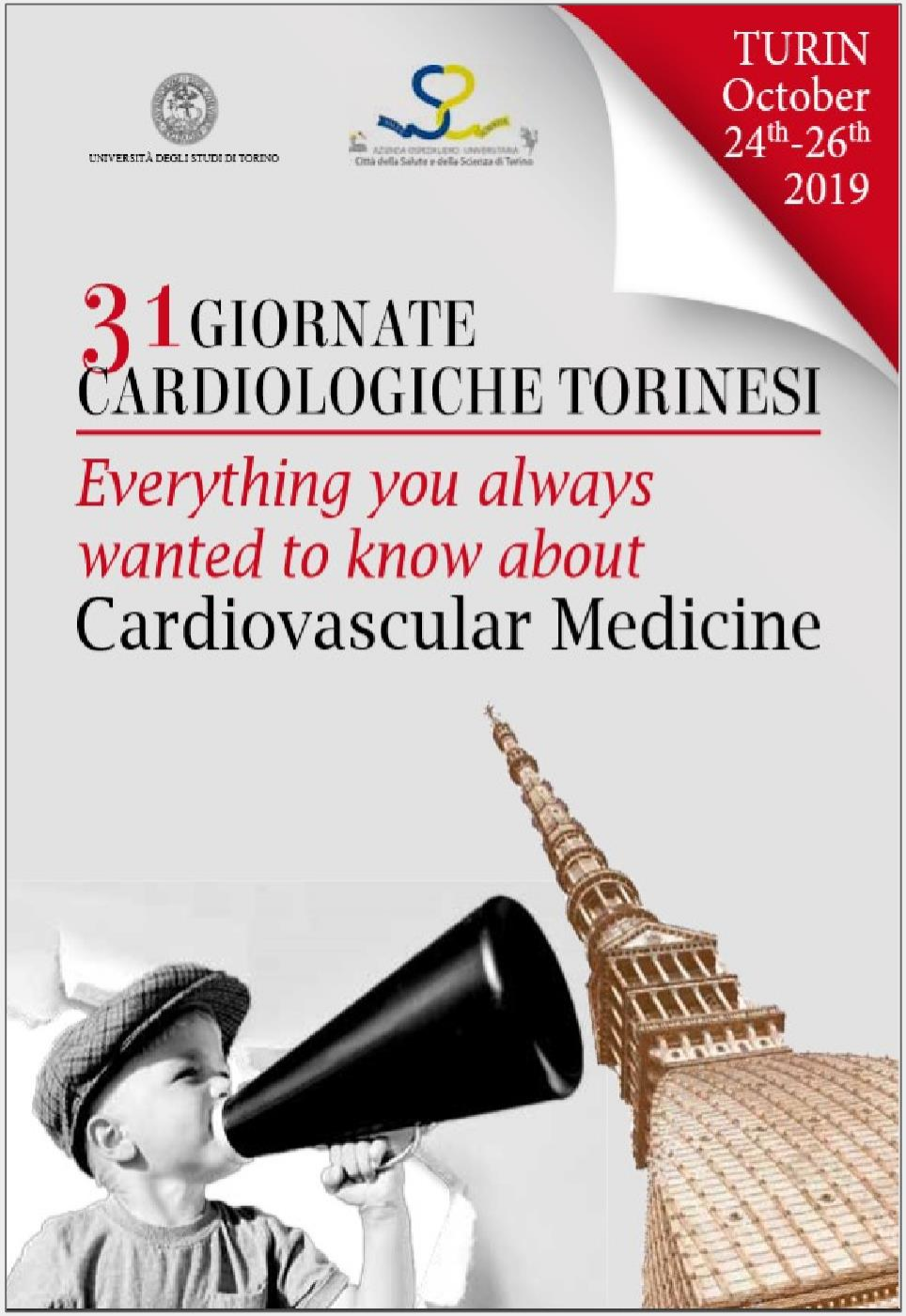


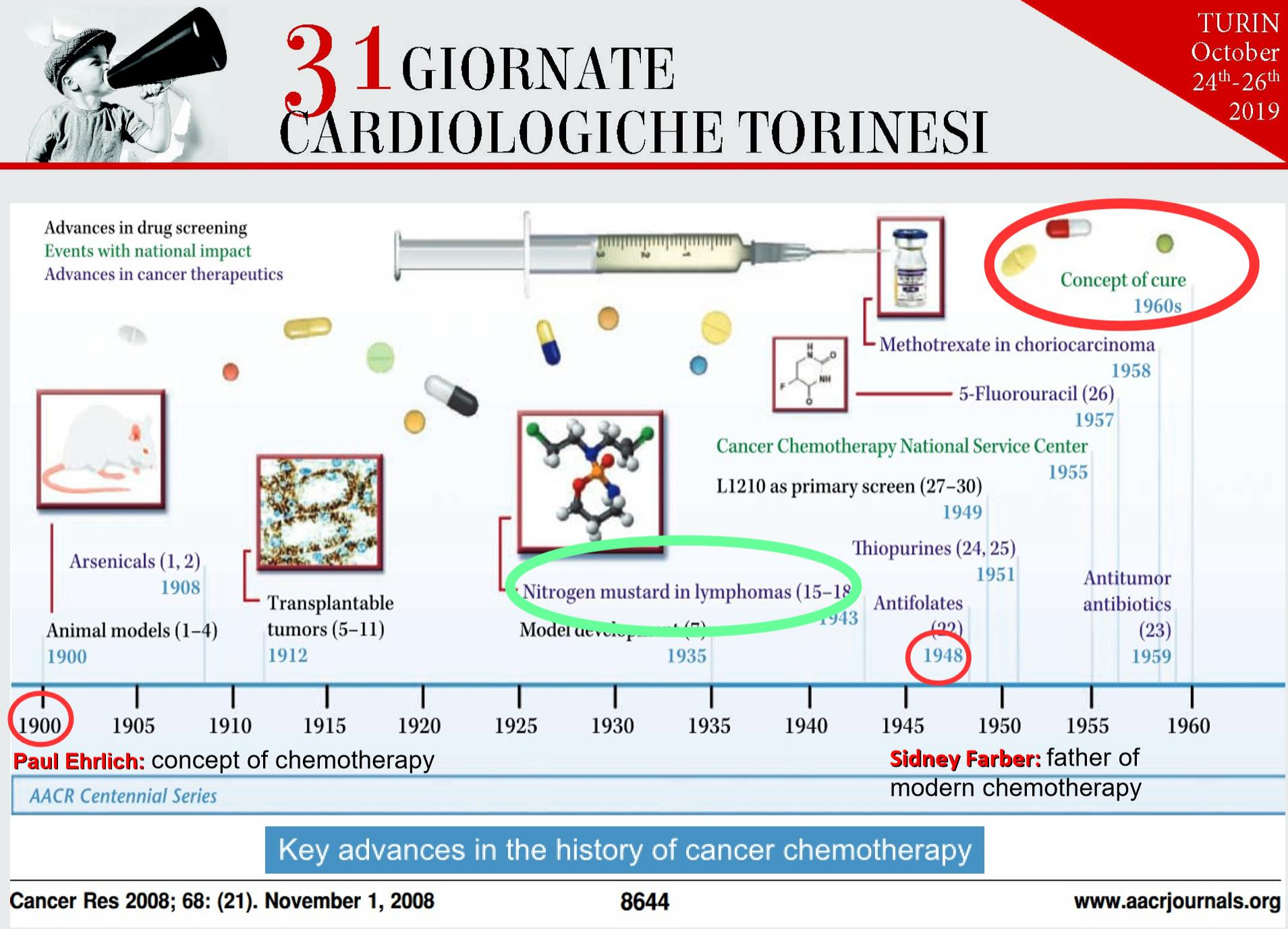
Sala
Vittoria

THURSDAY October 24th 2019
Afternoon

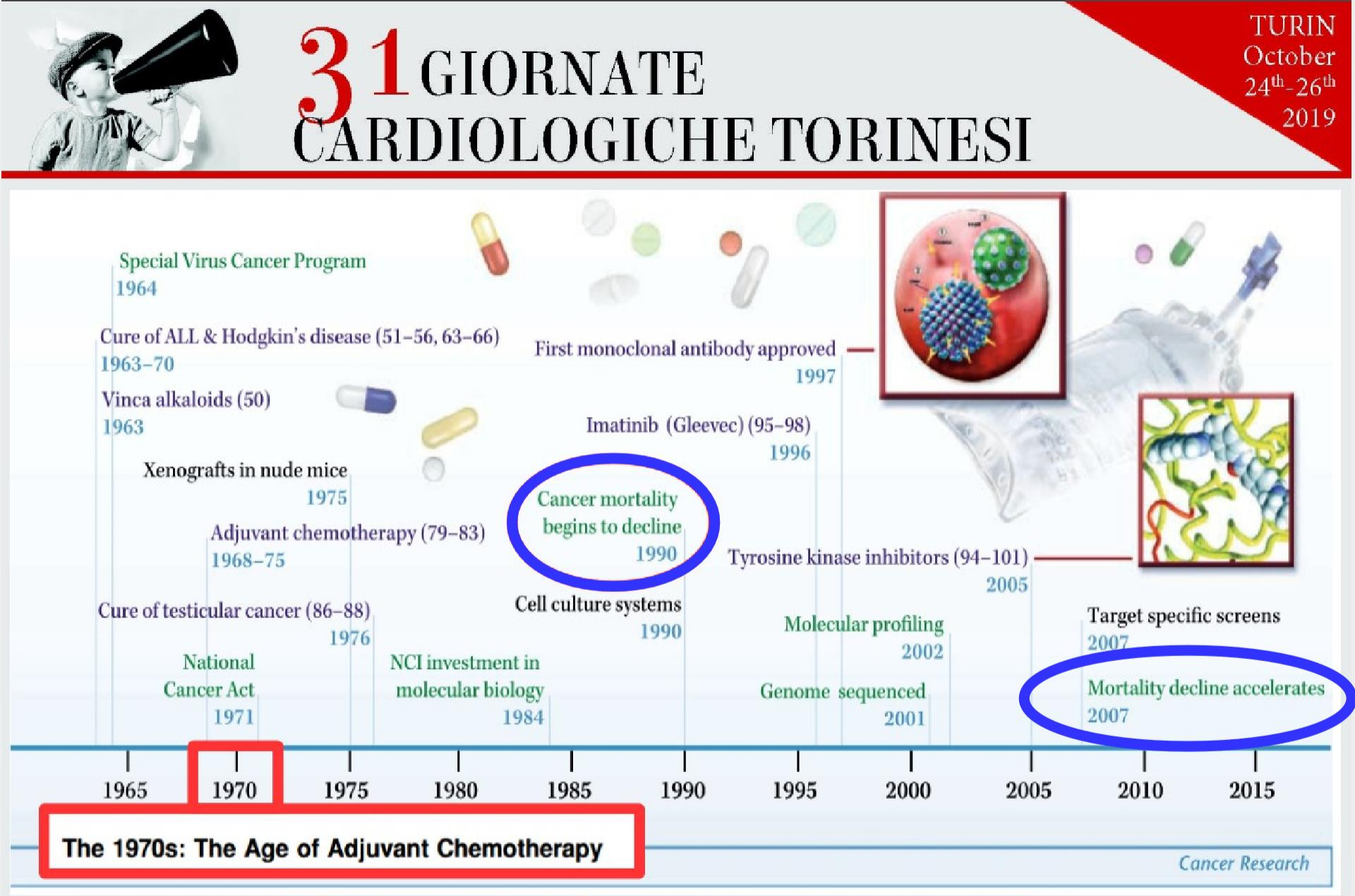
Oncology and Cardiotoxicity

Marinella Mistrangelo
Dipartimento Rete Oncologica
Piemonte e Valle d'Aosta

Città della Salute e della Scienza -Torino



Key advances in the history of cancer chemotherapy



Key advances in the history of cancer chemotherapy

ANTHRACYCLINES

Table 1: Mechanisms of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Specific Agents	FDA-Approved Indications	Proposed Mechanisms of Cardiotoxicity	Is Risk of Cardiac Toxicity Modified by Pre-Existing Cardiovascular Disease/ Risk Factors?	Is Risk of Cardiac Toxicity Dose-Dependent?
Anthracyclines	Doxorubicin Daunorubicin Epirubicin Idarubicin Mitoxantrone	Multiple myeloma Hodgkin disease Lymphoma Leukemia SCC of the head/ neck Tumors of the breast, ovary, prostate, stomach, thyroid, lung	Oxidative stress[73,74] Mitochondrial dysfunction[75,76] Mitochondrial iron accumulation[11] Interaction with Top2beta[12] Autophagy[13]	Yes	Yes

Table 2: Clinical Manifestations and Management of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Most Common Manifestations of Cardiotoxicity	Proposed Management Strategies	Clinical Trial Data to Guide Cardioprotective Therapy	Toxicity Permanent or Reversible?
Anthracyclines	LV dysfunction CHF	Substitute liposomal formulation Neurohormonal blockade Dexrazoxane Discontinuation of therapy for CHF	Neurohormonal blockade[4,19,20,22,79,80] Statins[81,82] Dexrazoxane[28]	Often permanent

Aarti Asnani, Randall T Peterson.

USC – US Cardiology Review - Volume 11 Issue 1 Spring 2017

Cancer Therapy–Induced Cardiotoxicity: Basic Mechanisms and Potential Cardioprotective Therapies

Virginia Shalkey Hahn, MD; Daniel J. Lenihan, MD; Bonnie Ky, MD, MSCE

Cardiotoxicity Due to Anthracyclines: Mechanisms and Potential Therapeutics

Anthracyclines are likely the most frequently cited and well-studied class of cardiotoxic anticancer agents, and although they are effective, their use is limited by dose-dependent toxicity.[10,11] Retrospective analyses from clinical trials in adults suggest that the incidence of congestive heart failure (HF) due to doxorubicin was 1.7% at a cumulative dose of 300 mg/m^2, 4.7% at 400 mg/m^2, 15.7% at 500 mg/m^2, and 48% at 650 mg/m^2.[10]

Smith *et al. BMC Cancer* 2010, **10**:337
http://www.biomedcentral.com/1471-2407/10/337

BMC Cancer

RESEARCH ARTICLE Open Access

Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials

Lesley A Smith*[1], Victoria R Cornelius[1], Christopher J Plummer[2], Gill Levitt[3], Mark Verrill[4], Peter Canney[5] and Alison Jones[6]

Results: Fifty-five published RCTs were included; the majority were on women with advanced breast cancer. A significantly greater risk of clinical cardiotoxicity was found with anthracycline compared with non-anthracycline regimens (OR 5.43 95% confidence interval: 2.34, 12.62), anthracycline versus mitoxantrone (OR 2.88 95% confidence interval: 1.29, 6.44), and bolus versus continuous anthracycline infusions (OR 4.13 95% confidence interval: 1.75, 9.72). Risk of clinical cardiotoxicity was significantly lower with epirubicin versus doxorubicin (OR 0.39 95% confidence interval: 0.20, 0.78), liposomal versus non-liposomal doxorubicin (OR 0.18 95% confidence interval: 0.08, 0.38) and with a concomitant cardioprotective agent (OR 0.21 95% confidence interval: 0.13, 0.33). No statistical heterogeneity was

Table 1: Mechanisms of Cardiotoxicity Associated with Cancer Treatments

FLUOROPYRIMIDINES

Type of Cancer Treatment	Specific Agents	FDA-Approved Indications	Proposed Mechanisms of Cardiotoxicity	Is Risk of Cardiac Toxicity Modified by Pre-Existing Cardiovascular Disease/ Risk Factors?	Is Risk of Cardiac Toxicity Dose-Dependent?
Fluoropyrimidines	5-Fluorouracil Capecitabine	Tumors of the colon, liver, pancreas, rectum, stomach, breast, ovary	Protein kinase C-mediated vasoconstriction[37] Impaired ROS handling[38] Direct endothelial toxicity[39]	Unknown	Not clearly established

Table 2: Clinical Manifestations and Management of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Most Common Manifestations of Cardiotoxicity	Proposed Management Strategies	Clinical Trial Data to Guide Cardioprotective Therapy	Toxicity Permanent or Reversible?
Fluoropyrimidines	Coronary vasospasm	Nitrates Calcium-channel blockers	None	Often reversible

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Table 1: Mechanisms of Cardiotoxicity Associated with Cancer Treatments

ANTI-HER2

Type of Cancer Treatment	Specific Agents	FDA-Approved Indications	Proposed Mechanisms of Cardiotoxicity	Is Risk of Cardiac Toxicity Modified by Pre-Existing Cardiovascular Disease/ Risk Factors?	Is Risk of Cardiac Toxicity Dose-Dependent?
Anti-HER2	Trastuzumab Pertuzumab Lapatinib	HER2-overexpressing breast cancer and metastatic gastric cancer	Antagonism of HER2 pathway[41,42]	Yes	No

Table 2: Clinical Manifestations and Management of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Most Common Manifestations of Cardiotoxicity	Proposed Management Strategies	Clinical Trial Data to Guide Cardioprotective Therapy	Toxicity Permanent or Reversible?
Anti-HER2	LV dysfunction CHF	Interruption or discontinuation of therapy Neurohormonal blockade	Neurohormonal blockade[22,83,84]	Often reversible

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Therapeutic Advances in Drug Safety Review

Cardiovascular toxicity associated with adjuvant trastuzumab therapy: prevalence, patient characteristics, and risk factors

Adedayo A. Onitilo, Jessica M. Engel and Rachel V. Stankowski

Prevalence of cardiotoxicity with trastuzumab treatment

function in the pivotal phase II and III trials of trastuzumab for the treatment of metastatic HER2-positive breast cancer, the independent Cardiac Review and Evaluation Committee (CREC) reported rates of cardiac dysfunction ranging from as low as 8% with trastuzumab alone to nearly 30% in patients treated with concomitant anthracycline and trastuzumab [Seidman *et al.* 2002]. Safety data from the rand-

Current Medical Research and Opinion
Volume 29, Issue 8, 2013

Oncology: Review
Cardiotoxicity of novel HER2-targeted therapies

LAPATINIB: 3689 patients enrolled in 49 trials.
- asymptomatic cardiac events were reported in 53 patients (1.4%)
- symptomatic grade III and IV systolic dysfunction was observed only in 7 patients (0.2%).

PERTUZUMAB: In phase I–III trials.
- cardiac dysfunction was seen in 4.5–14.5% usually grade I and II.

Cardiotoxicity of pertuzumab was usually reported with the trastuzumab combination and no additive cardiotoxicity was reported with addition of pertuzumab to trastuzumab.

Current Medical Research and Opinion
Volume 29, Issue 8, 2013

Oncology: Review
Cardiotoxicity of novel HER2-targeted therapies

T-DM1: had a better safety profile compared to trastuzumab.

- no significant cardiotoxicity was observed with T-DM1 in heavily pre-treated patients.
- EMILIA study:
  - only in **1.7%** of patients in the T-DM1 group experienced **reduction of left ventricular ejection fraction** (LVEF),
  - **grade III LVEF** reduction developed only in **one patient** (0.2%) in the T-DM1 group compared to the lapatinib plus capacitabine group.

NERATINIB: In phase I–II trials with neratinib no cardiotoxicity was reported whereas cardiotoxicity was seen between 0–5.3% with **afatinib** treatment.

VEGF INHIBITORS

Table 1: Mechanisms of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Specific Agents	FDA-Approved Indications	Proposed Mechanisms of Cardiotoxicity	Is Risk of Cardiac Toxicity Modified by Pre-Existing Cardiovascular Disease/ Risk Factors?	Is Risk of Cardiac Toxicity Dose-Dependent?
VEGF pathway inhibitors	Sunitinib Sorafenib Imatinib Dasatinib Nilotinib	Wide range of hematologic malignancies and solid tumors	Sunitinib: Depletion of coronary microvascular pericytes[77] Sorafenib: Inhibition of Raf-1/B-raf[78]	Likely	Varies by agent; not clearly established

Table 2: Clinical Manifestations and Management of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Most Common Manifestations of Cardiotoxicity	Proposed Management Strategies	Clinical Trial Data to Guide Cardioprotective Therapy	Toxicity Permanent or Reversible?
VEGF pathway inhibitors	Hypertension LV dysfunction CHF ACS QT prolongation	Hypertension: standard treatment; continue therapy. LV dysfunction, CHF, ACS: Interruption or discontinuation of therapy	None	Often reversible

Hypertension does appear to be an on-target effect, and in renal cell carcinoma, the development of hypertension correlates with increased efficacy of treatment and improved cancer outcomes.

Aarti Asnani, Randall T Peterson. USC – US Cardiology Review - Volume 11 Issue 1 Spring 2017

Table 1. Summary of grade 3–4 adverse cardiovascular events of FDA-approved anti-VEGF therapies in prospective phase I–III clinical trials (published up to December 2008)

	Hypertension				Left ventricular systolic dysfunction				Hemorrhagic/thrombotic complications			
Phase	**I**	**II**	**III**	**Total**	**I**	**II**	**III**	**Total**	**I**	**II**	**III**	**Total**
Bevacizumab												
Patients	170	1,519	3,075	4,764	170	1,519	3,075	4,764	170	1,519	3,075	4,764
Events	16	157	261	434	NR	4	11	15	12	165	282	459
Average, %	9.4	10.3	8.5	**9.2**	NR	0.3	0.4	**0.3**	7.0	11.0	9.2	**9.6**
Range, %	0–33	0–48	3–18		NR	0–12	0–3		0–18	0–32	3–23	
Sunitinib												
Patients	55	546	577	1178	55	546	577	1178	55	546	577	1178
Events	4	41	36	81	2[a]	7	7	16	3	11	NR	14
Average, %	7.3	7.5	6.2	**6.9**	3.6	1.3	1.2	**1.4**[b]	5.5	2.0	NR	**1.2**
Range, %	6–8	2–18	3–8		0–13	0–5	0–2		0–13	0–4	NR	
Sorafenib												
Patients	446	822	748	2016	446	822	748	2016	446	822	748	2016
Events	25	98	22	145	1	NR	NR	1	13	15	48	76
Average, %	6.0	12.0	3.0	**7.2**	0.2	NR	NR	**0.05**	3.0	2.0	6.4	**3.8**
Range, %	0–19	0–31	2–4		0–3	NR	NR		0–14	0–8	6–7	

Numbers in bold indicate cumulative average incidence for all phase I, II, and III clinical trials.
[a]Four patients were withdrawn from a phase I study with sunitinib because of decreased LVEF [55].
[b]In three retrospective studies, the rates of heart failure in patients treated with sunitinib were 3%, 8%, and 15%, respectively [65, 68, 69].
Abbreviations: FDA, U.S. Food and Drug Administration; LVEF, left ventricular ejection fraction; NR, not reported; VEGF, vascular endothelial growth factor.

The Oncologist 2010;15:130–141 www.TheOncologist.com

Cardiotoxicity

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multitargeted tyrosine kinase inhibitors. Sunitinib has been shown to prolong the QT interval, the PR interval, causing bradycardia, and to induce ST and T wave changes [22]. Torsade de pointes has been observed in <0.1% of patients receiving sunitinib. The effect of sunitinib on QT interval is dose dependent [23].

Annals of Oncology 21 (Supplement 7): vii173–vii179, 2010
doi:10.1093/annonc/mdq295

Table 3. Drugs producing prolonged QT interval

Antidepressants	Amitryptiline, clomipramine, desipramine, imipramine
Antibiotics	Clarithromycin, erythromycin, sparfloxacin, pentamidine
Antifungals	Ketoconazole, miconazole, itraconazole
Serotonin agonist/antagonist	Cisapride, ketaserin, zimeldine
Antipsychotics	Phenothiazine, droperidol, haloperidol
Antiarrhythmic drugs	IA: procainamide, quinidine, amaline, disopyramide
	IB: flecaine, propafenone
	III: amiodarone, sotalol, dofetilide, ibutilide
Vasodilators	Bepridil, perhexiline
Other	Methadone

Cardiotoxicity

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Annals of Oncology 21 (Supplement 7): vii173–vii179, 2010
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Cardiotoxicity

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Table 4. Risk factors for drug-induced QT interval prolongation and torsade des pointes

Gender	Female
Baseline ECG alteration	Baseline QT prolongation
	Subclinical long QT syndrome
Previous cardiovascular disease	Myocardial ischaemia
	Congestive heart failure
	Cardiac hypertrophy
	Myocarditis
	Bradycardia
	Atrioventricular block
Electrolyte disturbances	Hypokalaemia, hypomagnesaemia, hypocalcaemia
Endocrine disorders	Hypothyroidism, hyperparathyroidism, hyperaldosteronism
Neurological disorders	Subarachnoid haemorrhage
	Stroke
	Intracranial trauma
Other diseases	Diabetes, cirrhosis
Related to drug administration	High drug concentration
	Rapid rate of intravenous infusion with a QT-prolonging drug

Annals of Oncology 21 (Supplement 7): vii173–vii179, 2010
doi:10.1093/annonc/mdq295

IMMUNE CHECKPOINT INHIBITORS

Table 1: Mechanisms of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Specific Agents	FDA-Approved Indications	Proposed Mechanisms of Cardiotoxicity	Is Risk of Cardiac Toxicity Modified by Pre-Existing Cardiovascular Disease/ Risk Factors?	Is Risk of Cardiac Toxicity Dose-Dependent?
Immune checkpoint inhibitors	Nivolumab Pembrolizumab Atezolizumab Ipilimumab	Melanoma NSCLC RCC Head and neck cancer Hodgkin's lymphoma Bladder cancer	Under investigation	Unknown	Not clearly established; risk is likely increased with combination immune checkpoint inhibition

Table 2: Clinical Manifestations and Management of Cardiotoxicity Associated with Cancer Treatments

Type of Cancer Treatment	Most Common Manifestations of Cardiotoxicity	Proposed Management Strategies	Clinical Trial Data to Guide Cardioprotective Therapy	Toxicity Permanent or Reversible?
Immune checkpoint inhibitors	Myocarditis	Discontinuation of therapy Steroids Infliximab Antithymocyte globulin	None	Unknown

Aarti Asnani, Randall T Peterson.
USC – US Cardiology Review - Volume 11 Issue 1 Spring 2017

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.jfma-online.com

Review Article

Cardiovascular toxicity of immune checkpoint inhibitors in cancer patients: A review when cardiology meets immuno-oncology

Dong-Yi Chen [a,1], Wen-Kuan Huang [b,c,1], Victor Chien-Chia Wu [a,1], Wen-Cheng Chang [b,1], Jen-Shi Chen [b,1], Cheng-Keng Chuang [d,1], Pao-Hsien Chu [a,*,1]

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Table 1 Immune checkpoint inhibitors: cardiotoxic effects.

Molecular target	Drug	Cardiotoxicity reported
CTLA-4	Ipilimumab (YERVOY)	• MDX010-20 (melanoma): pericarditis[a] (incidence <1%, including fatal cases) • CA184-029 (melanoma): fatal myocarditis[a] (<0.1%) • Heart failure, Takotsubo syndrome
PD-1	Pembrolizumab (KEYTRUDA)	• Keynote-087 (Hodgkin's lymphoma): myocarditis[a] (0.5%) • Keynote-170 (PBMCL): myocardial infarction[a] (2%), pericardial effusion[a] (2%), pericarditis[a] (2%), arrhythmia[a] (4%), cardiac tamponade[a] (2%) • Keynote-006 (melanoma): heart failure[a] (incidence 0.4%) • Takotsubo syndrome
	Nivolumab (OPDIVO)	• CHECKMATE-037 (melanoma): ventricular arrhythmia[a] (1–10%) • Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab: myocarditis[a] (<1%), pericarditis[a] (<1%) • TB reactivation with pericarditis
PD-L1	Atezolizumab (TECENTRIQ)	• Myocarditis[a] (≤1.0%) • Myocardial infarction[a] • Cardiac arrest[a]
	Avelumab (BAVENCIO)	• Myocarditis[a] (<1%)
	Durvalumab (IMFINZI)	• Myocarditis[a] (<1%) • Takotsubo syndrome (combined with tremelimumab)
Combined anti-PD-1/anti-CTLA4	Nivolumab & Ipilimumab	• Myocarditis: significantly higher incidence rate in combination therapy compared with nivolumab alone (0.27% vs. 0.06%; $P < 0.001$)[b] • Takotsubo syndrome • Myocarditis: 2.4%[c]

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

[a] Included in the label of Food and Drug Administration label (up to date as of March 2019).

[b] In 2016, the Bristol-Myers Squibb corporate safety database revealed 18 cases (0.09%) of myocarditis among 20,594 patients being treated with nivolumab, ipilimumab or a combination of both.[5]

[c] Of the 964 patients at Massa-chusetts General Hospital who received an ICI between November 2013 and July 2017, 1.14% (11 patients) developed myocarditis.[6]

Cardiovascular toxicity of immune checkpoint inhibitors in cancer patients: A review when cardiology meets immuno-oncology

Dong-Yi Chen [a,1], Wen-Kuan Huang [b,c,1], Victor Chien-Chia Wu [a,1], Wen-Cheng Chang [b,1], Jen-Shi Chen [b,1], Cheng-Keng Chuang [d,1], Pao-Hsien Chu [a,*,1]

Conclusions and future directions

As ICI treatment has expanded to cover a variety of cancer types, there will be an increasing number of patients receiving this novel therapy. ICI-associated cardiotoxicity is relatively rare, however it can be serious and potentially fatal when it develops. Careful surveillance, prompt recognition and appropriate treatment of ICI-associated cardiac side effects will become increasingly important. Future research is required to clarify the predisposing risk factors for the development of cardiac side effects following ICI treatment; to understand the underlying mechanisms of ICI-associated cardiotoxicity; to develop appropriate monitoring protocols for the detection of early toxic effects; and to set up appropriate treatment

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Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

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BACKGROUND Myocarditis is an uncommon, but potentially fatal, toxicity of immune checkpoint inhibitors (ICI). Myocarditis after ICI has not been well characterized.

OBJECTIVES The authors sought to understand the presentation and clinical course of ICI-associated myocarditis.

METHODS After observation of sporadic ICI-associated myocarditis cases, the authors created a multicenter registry with 8 sites. From November 2013 to July 2017, there were 35 patients with ICI-associated myocarditis, who were compared to a random sample of 105 ICI-treated patients without myocarditis. Covariates of interest were extracted from medical records including the occurrence of major adverse cardiac events (MACE), defined as the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block.

RESULTS The prevalence of myocarditis was 1.14% with a median time of onset of 34 days after starting ICI (interquartile range: 21 to 75 days). Cases were 65 ± 13 years of age, 29% were female, and 54% had no other immune-related side effects. Relative to controls, combination ICI (34% vs. 2%; $p < 0.001$) and diabetes (34% vs. 13%; $p = 0.01$) were more common in cases. Over 102 days (interquartile range: 62 to 214 days) of median follow-up, 16 (46%) developed MACE; 38% of MACE occurred with normal ejection fraction. There was a 4-fold increased risk of MACE with troponin T of ≥1.5 ng/ml (hazard ratio: 4.0; 95% confidence interval: 1.5 to 10.9; $p = 0.003$). Steroids were administered in 89%, and lower steroids doses were associated with higher residual troponin and higher MACE rates.

CONCLUSIONS Myocarditis after ICI therapy may be more common than appreciated, occurs early after starting treatment, has a malignant course, and responds to higher steroid doses. (J Am Coll Cardiol 2018;71:1755–64)

Conclusions

Table 2 Cardiovascular toxicity due to antineoplastic drugs

Cardiovascular toxicity	Associated drugs
Heart failure	Doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone
	Cyclophosphamide, ifosfamide
	Docetaxel
	Trastuzumab, bevacizumab
	Sunitinib, pazopanib, sorafenib, imatinib, dasatinib, lapatinib, nilotinib
	Carfilzomib, Bortezomib
Myopericarditis	Cyclophosphamide
	5-fluorouracil, cytarabine
	Trastuzumab, rituximab
	Interleukin-2
	Immune-checkpoint inhibitors
Ischemic cardiomyopathy	5-fluorouracil, capecitabine
	Cisplatin
	Paclitaxel, docetaxel
	Etoposide
	Bebacizumab
	Sorafenib, sunitinib
	Bleomycin
Atrial fibrillation	Cisplatin
	Cyclophosphamide, ifosfamide, melphalan
	Doxorubicin
	Capecitabine, 5-FU
	Gemcitabine
	Etoposide
	Paclitaxel
	Rituximab
	Sorafenib, sunitinib, ibrutinib
	Bortezomib
	Interleukin-2, interferon
Bradyarrhythmias	Cisplatin
	Cyclophosphamide, ifosfamide
	Doxorubicin, epirubicin, mitoxantrone
	Capecitanina, 5-FU
	Gemcitabine
	Paclitaxel
	Thalidomide
	Imatinib, bortezomib
	Rituximab
	Arsenic trioxide, interleukin-2
Accelerated atherosclerosis	Bevacizumab, nilotinib, ponatinib
	Carfilzomib, bortezomib

Conclusions

Pericardial effusion	Cyclophosphamide Immune-checkpoint inhibitors[1]
Venous thromboembolic disease	5-fluorouracil Cisplatin Nilotinib, ponatinib, erlotinib Bevacizumab Vorinostat L-Asparaginase Immune-checkpoint inhibitors
Arterial thromboembolic disease	Cisplatin, carboplatin Gemcitabine Bleomycin Vincristine Nilotinib, ponatinib Bevacizumab Interferon alfa-2 Immune-checkpoint inhibitors
Arterial hypertension	Bevacizumab Sorafenib, sunitinib, axitinib, vandetanib, regorafenib
Pulmonary hypertension	Dasatinib Cyclophosphamide
Prolonged QT interval	Doxorubicin Depsipeptide, vorinostat Axitinib, cabozantinib, crizotinib, dasatinib, lapatinib, nilotinib, sorafenib, sunitinib, vandetanib, vemurafenib, ribociclib Arsenic trioxide

Clinical and Translational Oncology (2019) 21:94–105

Conclusions

1. Cardiovascular disease and second cancers are the most common cause of mortality in cancer survivors
2. **Longterm survivors** that have been treated with cardiotoxic treatments or radiotherapy **should be informed of their increased risk for cardiovascular diseases** (CVDs).
3. **Cardiovascular screening reduces the incidence of heart failure by 18%**, but there is a lack of agreement about the optimal test for screening and frequency of testing.
4. During follow-up, education in **long-term cancer survivors should be based on lifestyle modifications**, to prevent and treat CV risk factors, and instructions to report early CV signs and symptoms

Conclusions

Clinical management of these toxicities with the aid of multidisciplinary protocols

for prevention, diagnosis, and treatment, decreases unnecessary antitumor treatment discontinuation and optimizes global patient's outcomes.

NEW DRUGS...

The FDA approved or added new indications to 59 drugs or biologics for oncology in 2017, 47 in 2018, 20 such approvals in oncology have already been made in 2019.

Grazie per l'attenzione e buon proseguimento!