

Cœur et chimiothérapie

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Introduction

Avancée dans la thérapeutique des anticancéreux



Amélioration du suivi patient

-Morbimortalité reste élevée

-Atteints cardiovasculaires :+ + fréquentes

-Anthracyclines: Doxorubicine

-Alkylants: Cyclophosphamide (Endoxan*)

-Thérapies ciblées:

- Ac monoclonaux: inhibiteur HER
Trastuzumab: Herceptine*
- Inhibiteur Tyrosine kinase (Inhibiteur VEGF)
Sunitinib: Sutent*

Cas clinique

- Homme, 49 ans
- Thymome malin
- Chimiothérapie par les Anthracyclines + radiothérapie
- 3^{ème} lignée : Sutent* (**SUNITINIB**)

ETT réalisée avant le traitement : **Bonne fonction systolique du VG**

Risque cardiovasculaire ?

Le principal risque cardiovasculaire de ce patient débutant le sunitinib est:

- **A: HTA**
- **B: Arythmie**
- **C: Insuffisance cardiaque**
- **D: syndrome coronaire aigu**
- **E: aucun**

Le risque cardiovasculaire de ce patient qui débute son traitement par sunitinib est :

- **A: rare**
- **B: imprévisible**
- **C: prévisible mais rare**
- **D: prévisible et fréquent**
- **E: certain**

Comment détecter la dysfonction VG du précocément?

- **A: symptômes**
- **B: dosage de cTnT ou cTnI avant chaque cure**
- **C: série de dosages de cTnT ou cTnI après chaque cure**
- **D: série de dosages de NT-proBNP après chaque cure**
- **E: Echographie-doppler 2D or 3D + strain**

Seuils de détection écho de la cardiotoxicité débutante:

Mesure de la FEVG

- **A: diminution de 20 points par rapport limite inf. normale**
- **B: diminution de 15 points par rapport limite inf. normale**
- **C: diminution de 10 points par rapport limite inf. normale**
- **D: variation de 15% par rapport à la valeur initiale**
- **E: variation de 10% par rapport à la valeur initiale**

Seuils de détection écho de la cardiotoxicité débutante:

Mesure du strain longitudinal global

- **A: diminution de 10 points par rapport limite inf. normale**
- **B: diminution de 10 points par rapport valeur initiale**
- **C: diminution relative de 15% par rapport limite inf. normale**
- **D: diminution relative de 15% par rapport valeur initiale**
- **E: diminution relative de 10% par rapport limite inférieure normale**

Conduite à tenir?

Réduction de FEVG de 65% à 55%

- **A: Poursuite du traitement et contrôle après cure suivante**
- **B: changement de traitement anti-cancéreux**
- **C: décaler le traitement et contrôle écho 15-21j plus tard**
- **D: débiter IEC (ou ARA-II) et β -**

Conduite à tenir?

Réduction de FEVG de 58% à 49%

- **A: Poursuite du traitement et contrôle après cure suivante**
- **B: changement de traitement anti-cancéreux**
- **C: décaler le traitement et contrôle écho 15-21j plus tard**
- **D: débiter IEC (ou ARA-II) et β - et contrôle écho 15-21j plus tard**

Cette dysfonction VG est-elle réversible?

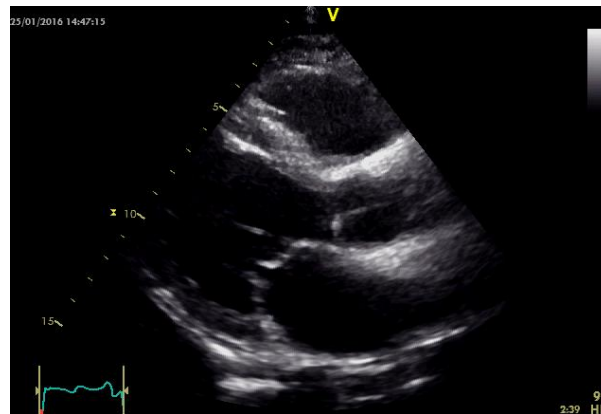
- **A: Non jamais**
- **B: Oui toujours**
- **C: Souvent**
- **D: Parfois**

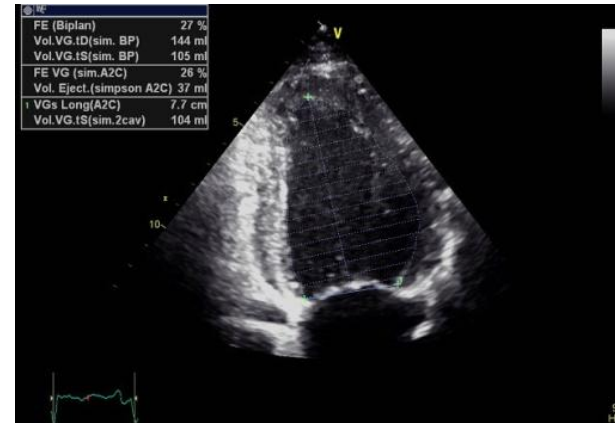
Cas clinique

- ♂, 49 ans
- Thymome maligne
- Chimiothérapie par Anthracycline +
Radiothérapie
- 3^{ème} lignée de chimiothérapie: Sutent*
(**SUNITINIB**)

Fonction systolique du VG était
conservée avant le traitement

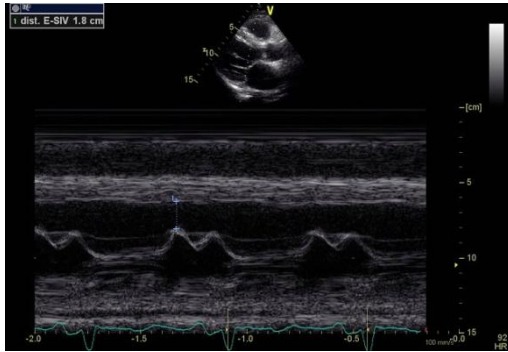
1 mois après la première cure de sunitinib → Insuffisance cardiaque aigue



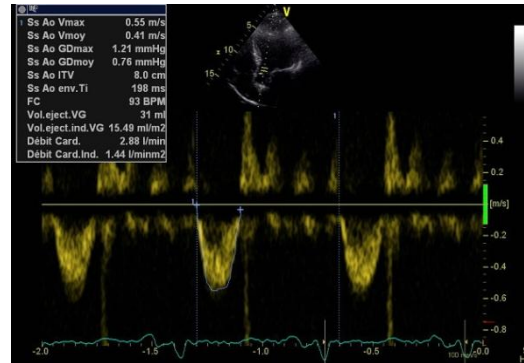


FEVG = 27%

(Biplan Simpson)



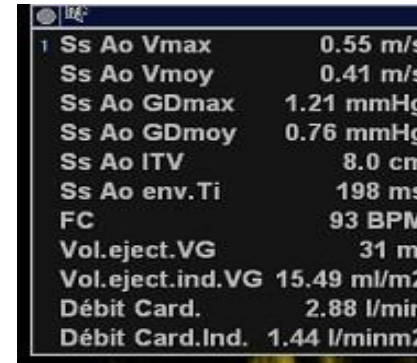
E- septum > 11mm



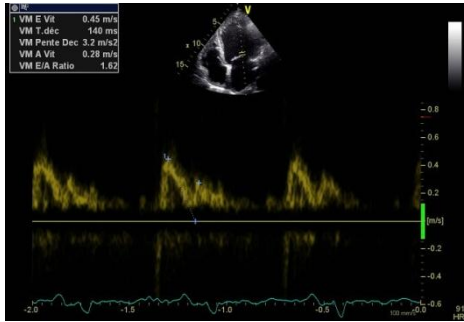
ITV Ao

Volume éjection systolique

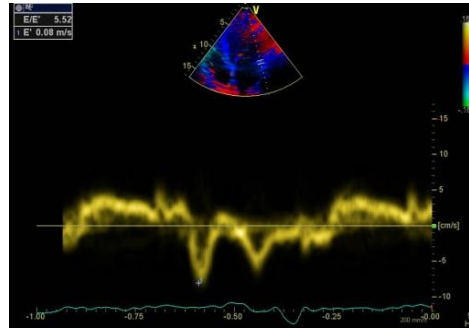
Débit cardiaque



$$0.8 < E/A < 2$$

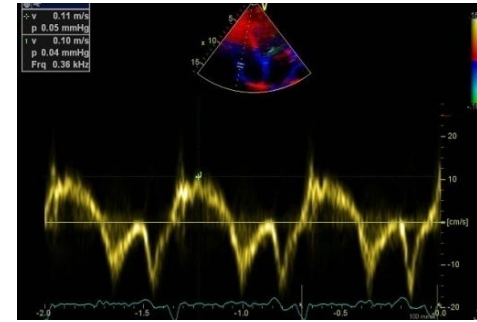


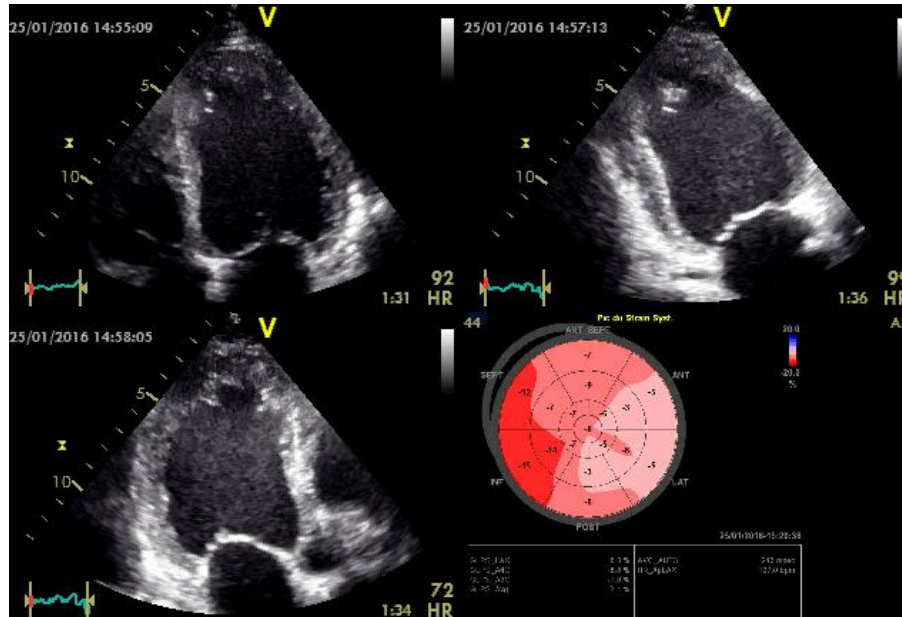
$$E/E' < 8$$



**Pressions de
remplissage élevées**

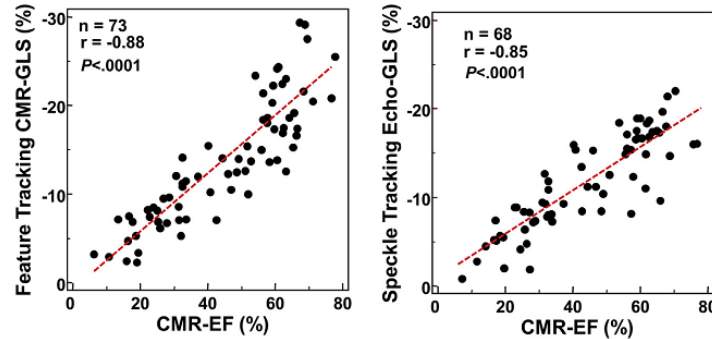
**Fonction VD
conservée**





Global Longitudinal Strain and Global Circumferential Strain by Speckle-Tracking Echocardiography and Feature-Tracking Cardiac Magnetic Resonance Imaging: Comparison with Left Ventricular Ejection Fraction

Toshinari Onishi, MD, Samir K. Saha, MD, Antonia Delgado-Montero, MD, Daniel R. Ludwig, MD, Tetsuaki Onishi, MD, Erik B. Schelbert, MD, MS, David Schwartzman, MD, and John Gorcsan, III, MD, *Pittsburgh, Pennsylvania; and Stockholm, Sweden*



$$\text{FEVG} = 3 \times \text{GLS} + 8 \%$$

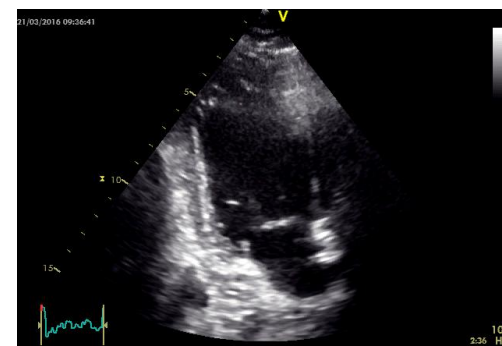
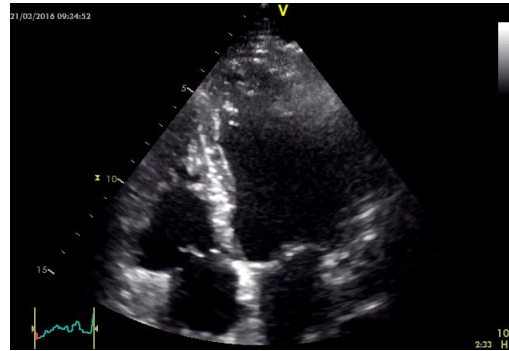
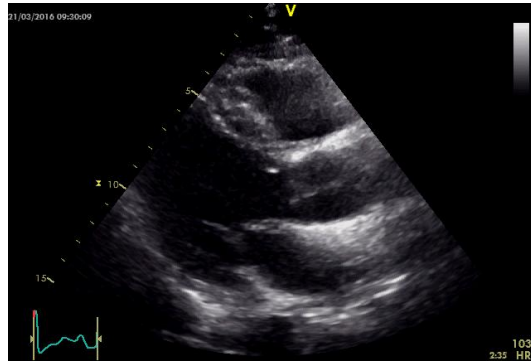
GLS < - 11%

FEVG < 35%

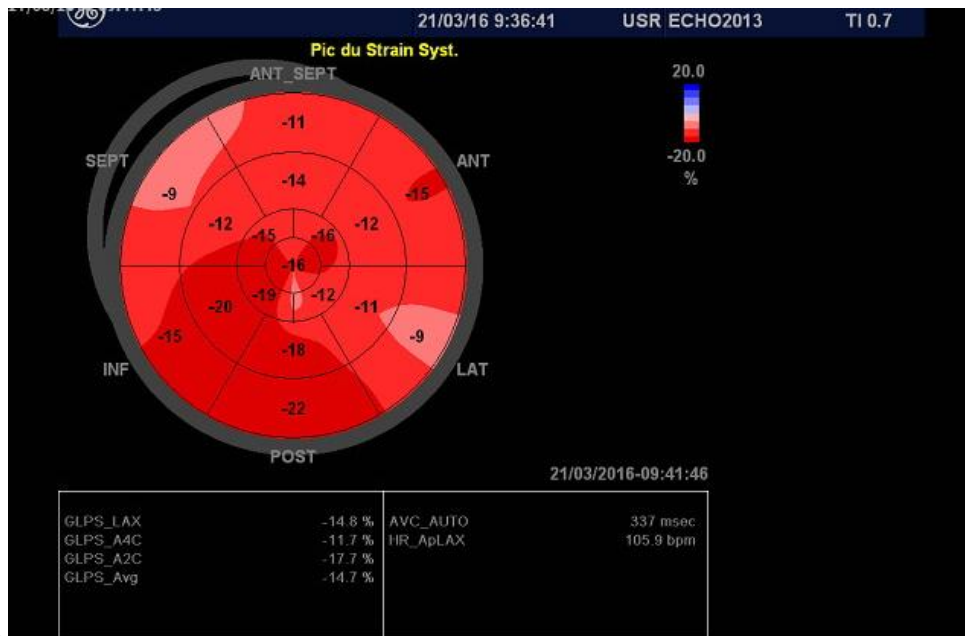
- Hospitalisation
- O2
- Diurétiques : Furosemid (IV)
- IEC: Ramipril
- BB : Bisoprolol

Bonne évolution clinique

Echocardiographie 2 (2 mois après)



Echocardiographie 2



GLS = -14.7%

ICA



2 Mois après trt



FEVG = 27%

GLS = -7.1%

FEVG = 54 %

GLS = -14.7%

Sunitinib : Inhibiteur de la Tyrosine Kinase (TKI).

Indications

- Tumeurs gastro-intestinal
- Kc du rein
- Kc du pancréas

Effets cardiovasculaires

- HTA
- SCA
- Arythmie
- QT long
- **Insuffisance cardiaque - dysfonction VG**

I C aigue après administration Sunitinib

Réversibilité sous IEC et BB

Intérêt d'identifier les patients à risque

**Position Paper
on cancer treatments
and cardiovascular toxicity
developed under the auspices
of the ESC Committee
for Practice Guidelines**

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

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www.escardio.org/guidelines



Incidence of left ventricular dysfunction associated with chemotherapy drugs

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m ² 550 mg/m ² 700 mg/m ²	3–5 7–26 18–48
Idarubicin (>90 mg/m ²)	5–18
Epirubicin (>900 mg/m ²)	0.9–11.4
Mitoxanthone >120 mg/m ²	2.6
Liposomal anthracyclines (>900 mg/m ²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m ² 12.5–16 g/m ²	0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1

Chemotherapy agents	Incidence (%)
Monoclonal antibodies	
Trastuzumab	1.7–20.1
Bevacizumab	1.6–4
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellaneous	
Everolimus	<1
Temsirolimus	<1

Factors associated with risk of cardiotoxicity following treatment with anthracyclines

Risk factors

- Cumulative dose
- Female sex
- Age
 - >65 years old
 - Paediatric population (<18 years)
- Renal failure
- Concomitant or previous radiation therapy involving the heart
- Concomitant chemotherapy
 - alkylating or antimicrotubule agents
 - immuno- and targeted therapies
- Pre-existing conditions
 - Cardiac diseases associating increased wall stress
 - Arterial hypertension
 - Genetic factors

Factors associated with risk of cardiotoxicity following anti-HER2 compounds and VEGF inhibitors

Agent	Risk factors
Anti-HER2 compounds	
- Antibodies - Trastuzumab - Pertuzumab - T-DM1 - Tyrosine kinase inhibitor - Lapatinib	- Previous or concomitant anthracycline treatment (<i>short time between anthracycline and anti-HER2 treatment</i>) - Age (>65 years) - High BMI >30 kg/mg² - Previous LV dysfunction - Arterial hypertension - Previous radiation therapy
VEGF inhibitors	
- Antibodies - Bevacizumab - Ramucirumab - Tyrosine kinase inhibitors - Sunitinib - Pazopanib - Axitinib - Neratinib - Afatinib - Sorafenib - Dasatinib	- Pre-existing HF, significant CAD or left side VHD (e.g. mitral regurgitation), chronic ischaemic cardiomyopathy - Previous anthracycline - Arterial hypertension - Pre-existing cardiac disease

Baseline risk factors for cardiotoxicity

<i>Current myocardial disease</i>	<i>Demographic and other CV risk factors</i>
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial Involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia
<i>Previous cardiotoxic cancer treatment</i>	<i>Lifestyle risk factors</i>
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

Anthracycline equivalence dose considering doxorubicin in rapid infusion as a reference

Drug	Relative cardiotoxicity	Incidence of HF rises to >5% when cumulative dose exceeds (mg/m ²)
Doxorubicin rapid infusion	1	400
Epirubicin	0.7	900
Daunorubicin	~0.75	800
Idarubicin	0.53	150

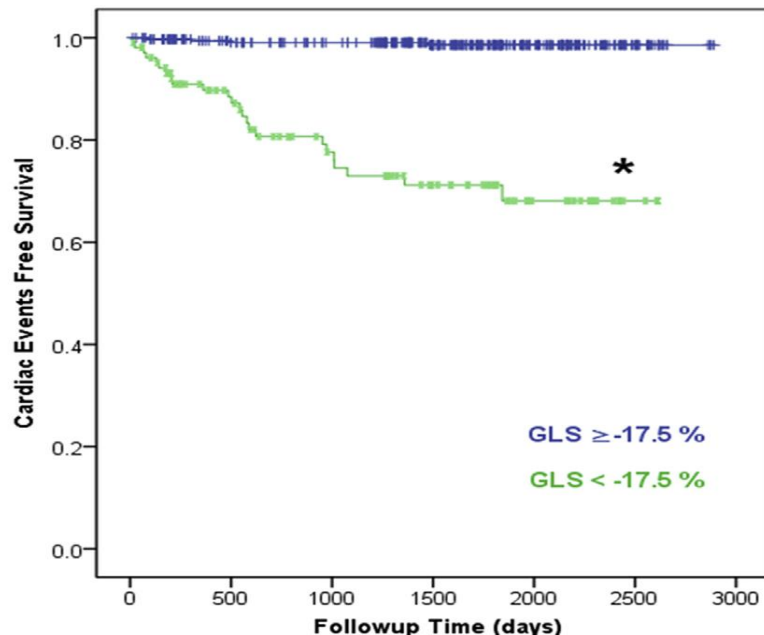
Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: – 3D-based LVEF – 2D Simpson's LVEF – GLS	- LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. - GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	- Wide availability. - Lack of radiation. - Assessment of haemodynamics and other cardiac structures.	- Inter-observer variability. - Image quality. - GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	>10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	Reproducibility.	- Cumulative radiation exposure. - Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	- Accuracy, reproducibility. - Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	- Limited availability. - Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: – Troponin I – High-sensitivity Troponin I – BNP – NT-proBNP	- A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. - Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.	- Accuracy, reproducibility. - Wide availability. - High-sensitivity.	- Insufficient evidence to establish the significance of subtle rises. - Variations with different assays. - Role for routine surveillance not clearly established.

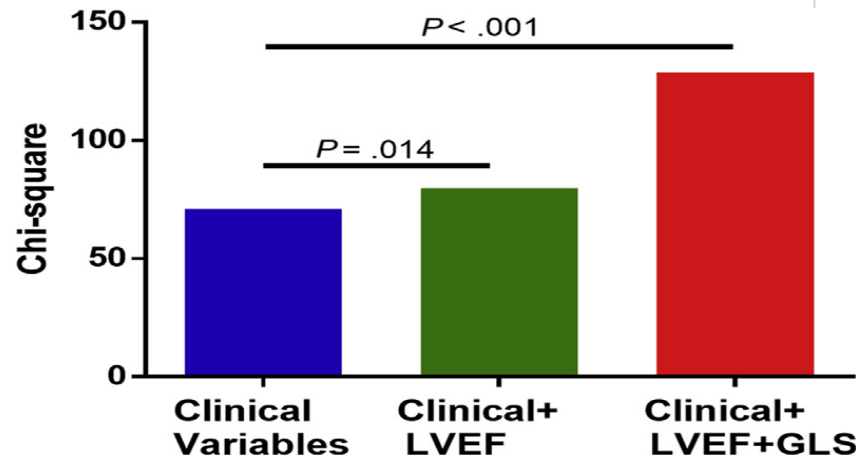
Myocardial strain imaging for early detection of chemotherapy-induced LV dysfunction (J Am Coll Cardiol 2015; 63: 2751)

- **10 to 15% early reduction in GLS**
- **Predictive of subsequent toxicity**
 - **<8% not significant**
 - **>15% predictive**
- **Coupled to serial cTn determinations**

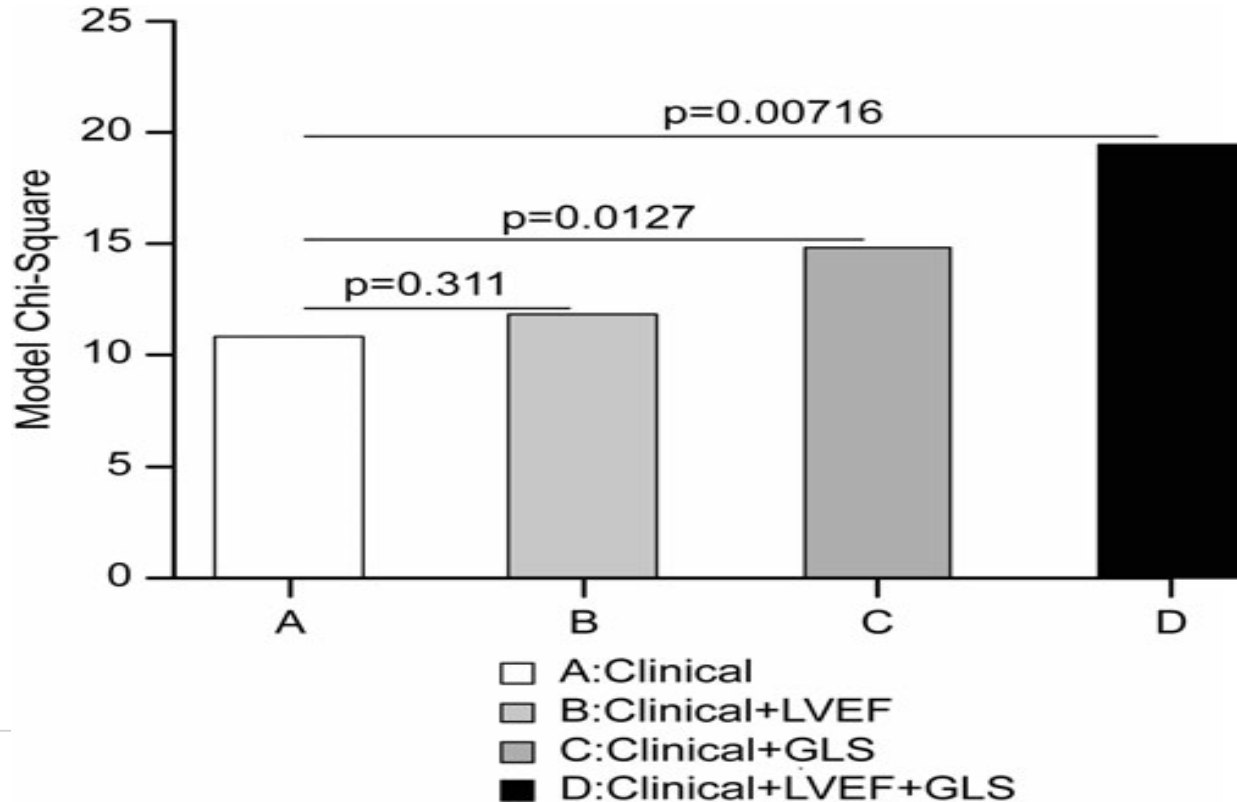
Myocardial strain is associated with adverse cardiac events in 450 pts treated with anthracyclines (JASE 2016; 29: 522)



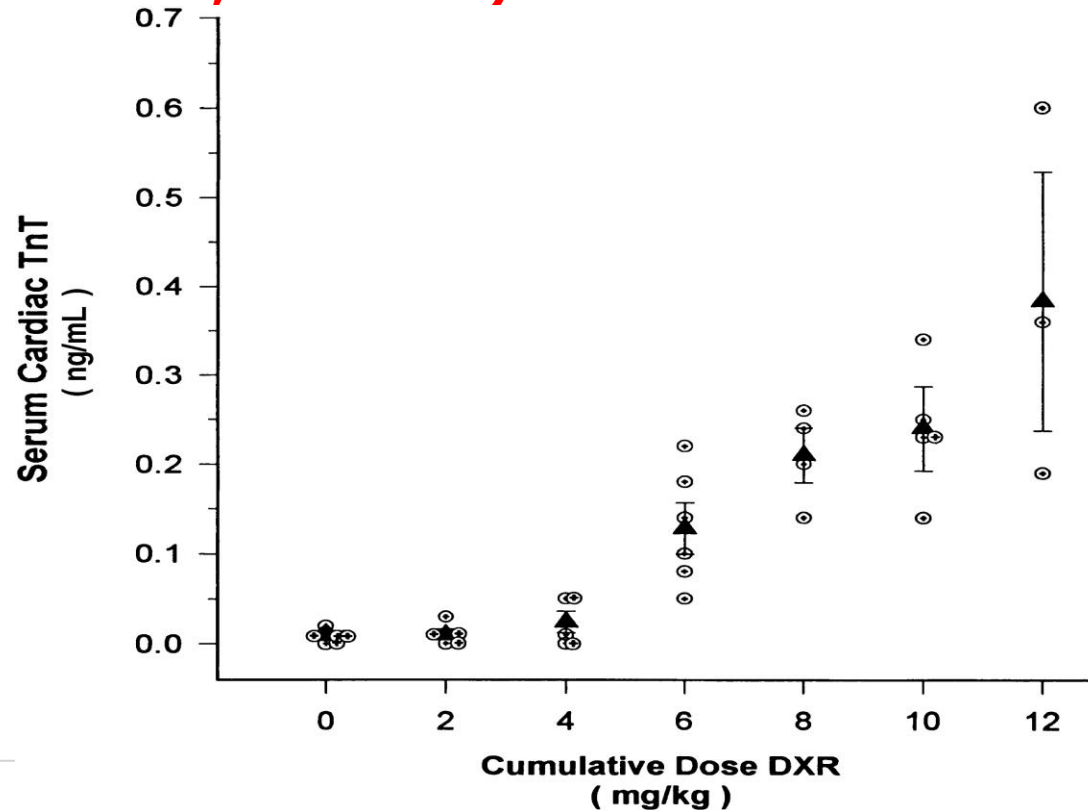
Pts with GLS ≥ -17.5	345	298	275	203	100	27	0
Pts with GLS < -17.5	105	72	52	37	17	3	0



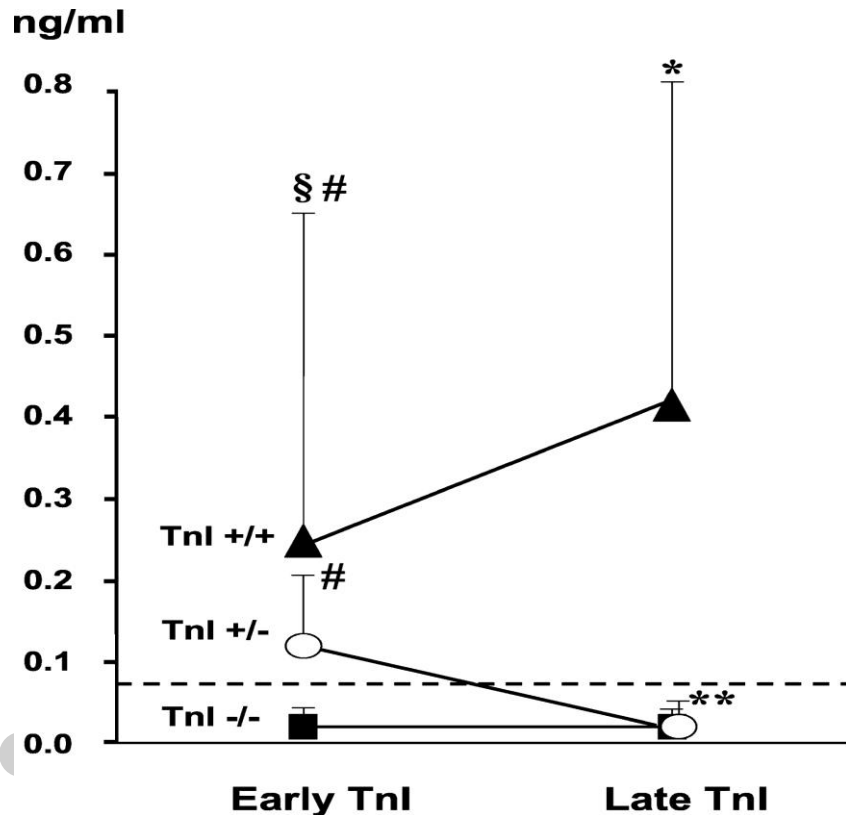
Predictive value of LVEF and GLS for HF in pts with anthracyclines and EF 50-59% (Eur Heart J CV Imaging 2015; 16: 977)



Dose-dependent increase of troponin T in DOX treated rats (Herman, JCO 1999, 17: 2237)



Troponin I in 703 cancer patients (Cardinale, Circulation 2004,109: 2749)



- Early and at 1 month
- TnI - < 0.08 ng/ml
- LVEF: 1, 3, 6, 12 mo
- **Cardiac events at FU:**
 - 498 pts TnI -/- : **1%**
 - 145 pts TnI +/- : **37%**
 - 63 pts TnI +/+ : **84%**

5 determinations in 3 days following the cycle,
The highest value being retained for analysis
1 additional determination 3 months later

Brain natriuretic peptides

- Increase in pts with impaired LVEF
- (De Vries, Okumura)
- Serial measurement for preventive purpose:
- 30 NHL: increase if LVEF reduced
(Eur J Haematol 1999, 62: 135)
- 107 pts with DOX: 19 % of pts with a decrease in LVEF: **BNP was not predictive**
(Eur J Heart Failure 2005,7: 87)

6 serial plasma NT-proBNP levels during a 72-hour period following cancer chemotherapy (Clin Chem 2005; 51:1405)

	No change	Transient increase , normal level at 72hrs	Persistent increase at 72hrs
Patients (%)	31%	35%	33%
Decline in LVEFat 12 months			Decrease from 66% to 45%

Drug	Brand name	Target	Approved clinical use
dasatinib	Sprycel	BCR-ABL, CD117 (c-kit), PDGFR	CML
erlotinib	Tarceva	EGFR	Non small cell lung and pancreatic cancer
Imatinib (nilotinib, ponatinib)	Gleevec	BCR-ABL, CD117 (c-kit), PDGFR	CML
lapatinib	Tykerb	EGFR, HER2 neu	HER2neu+ breast cancer
sunitinib	Sutent	VEGFR, PDGFR, CD117, CSF-1, FLT3	Renal cell cancer, GI stromal tumors
sorafenib	Nexavar	EGFR, VEGFR, PDGFR	Renal cell cancer, hepatocarcinoma
Crizotinib		ALK	Non small cell lung, NHL
ibrutinib		Bruton's TK	Mantle cell (B) NHL

Pathophysiological mechanisms of coronary artery disease in cancer treatment

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	• Endothelial injury • Vasospasm	• Up to 18% manifest myocardial ischaemia • Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	• Procoagulant status • Arterial thrombosis	• 20-year absolute risk of up to 8% after testicular cancer • 2% risk of arterial thrombosis
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	• Procoagulant status • Arterial thrombosis • Endothelial injury	• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiotherapy	• Endothelial injury • Plaque rupture • Thrombosis	• 2–7-fold increased relative risk of myocardial infarction • Cumulative 30-year coronary events incidence of 10% in Hodgkin lymphoma survivors • Risk proportional to irradiation dose

How are CVRF, CAD, drug combination and increased cardiac toxicity linked (Circulation 2016, 133:1272)

VEGF signaling and ACS

- **Bevacizumab: 2%**
- **Tki:**
 - **sunitinib: 5.9%**
 - **sorafenib: 2.3%**
 - **pazopanib: 7.6%**

Bcr-Abl linked Tki: rapidly progressive atherosclerosis:

- **Nilotinib: 2-25%**
- **Ponatinib: 9-48%**

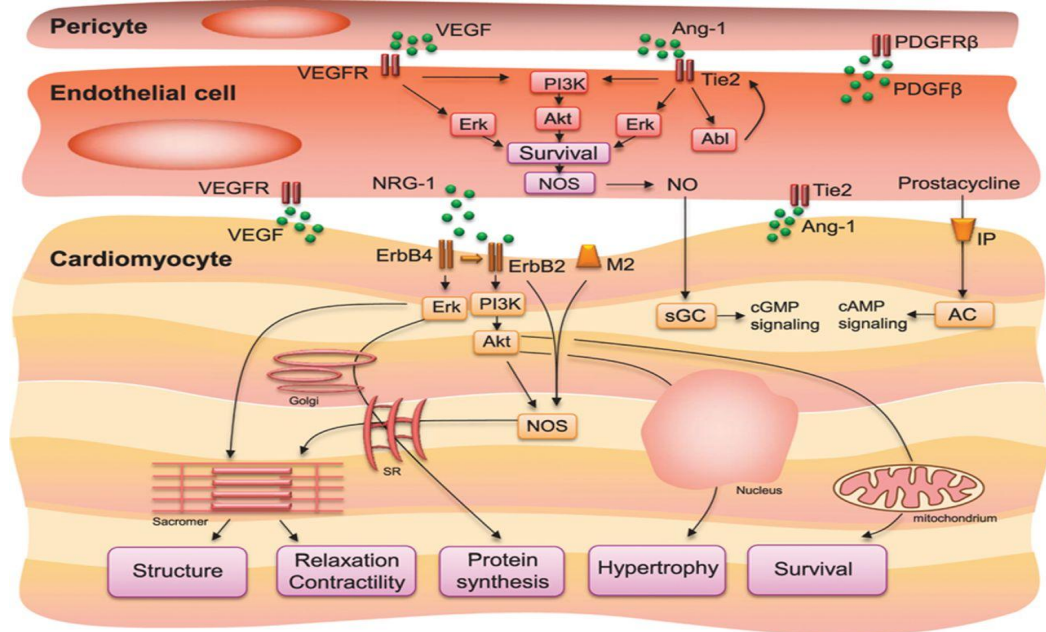
Abl kinases are required for vascular function (PNAS 2013; 110: 12432)

- **Experimental loss of endothelial cells' Abl**
= cardiomegaly, vascular defects
- **Abl required for functional endothelial cells**
 - *VEGF stimulates Abl*
 - *Abl involved in the prosurvival effect of VEGF on endothelial cells*

New insights into microvascular biology and cardiac toxicity of cancer therapy (Circulation 2016, 133:1272)

Sunitinib-treated mice:

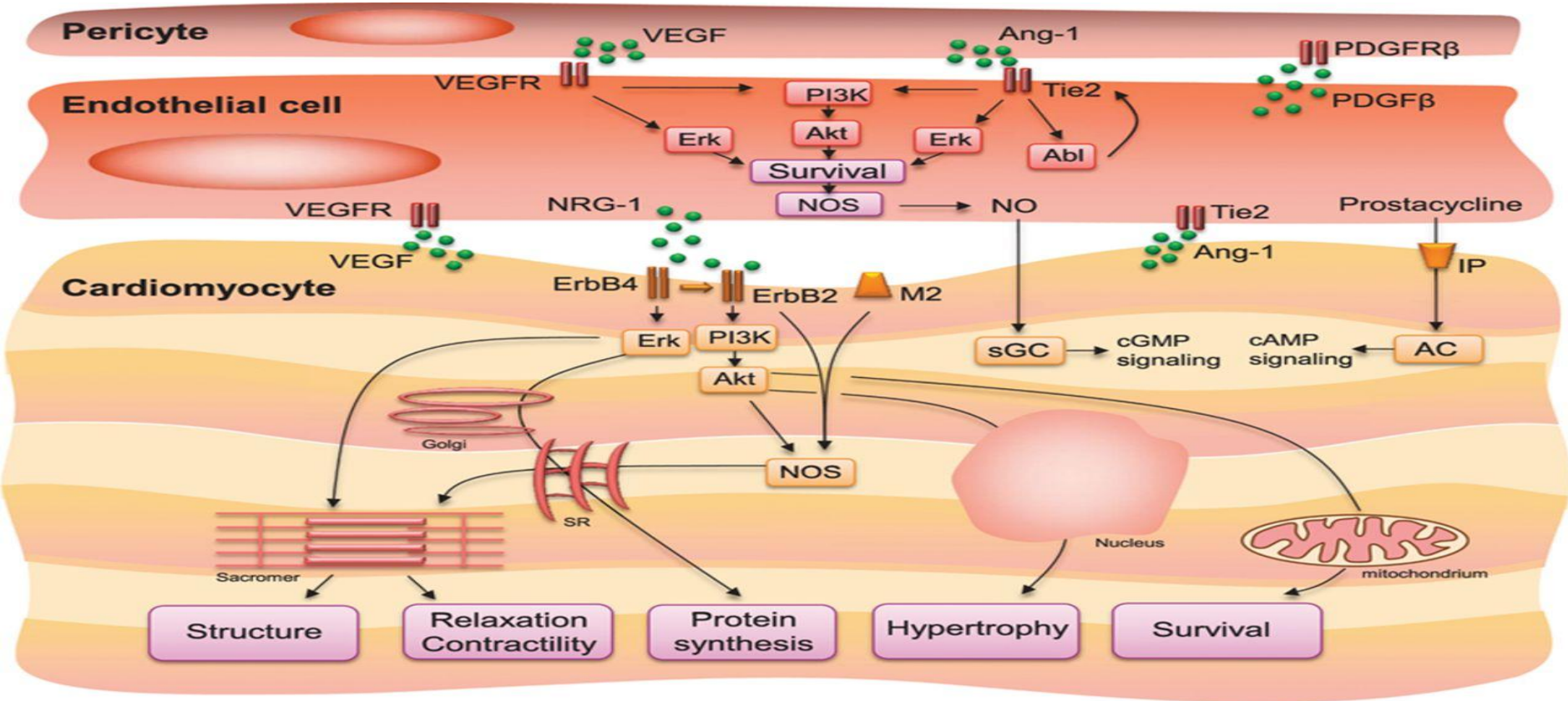
- Rarefication of microvascular pericytes
- No change in capillary density
- Microvascular dysfunction
- Reduced coronary flow reserve
- Reduced cardiac function



**Mice with cardiomyocytes or endothelial cells
deleted in VEGF
(Circulation 2016, 133:1272)**

- Lower myocardial microvascular density
- Cardiomyopathy
- Reversed by VEGF repletion
- *(similar to downregulation of VEGF in diabetic cardiomyopathy)*
- Mice with inducible defect in PDGFR- β
- Don't increase microvascular density after stress
- Reduced coronary perfusion, coronary flow reserve, and cardiac function

New insights into microvascular biology and cardiac toxicity of cancer therapy (Circulation 2016, 133:1272)



Cancer drug agents associated with cardiac arrhythmias

Type of arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicine, epirubicine, 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.
Sinus tachycardia	Anthracyclines, carmustine.
Atrioventricular block	Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.
Conduction disturbances	Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.
Atrial fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.
Supraventricular tachycardias	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5-FU, methotrexate), bortezomib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine), arsenic trioxide, doxorubicin, interferons, IL-2, methothrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.
Sudden cardiac death	Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nilotinib, romidepsin.

Cancer drug agents associated with QT prolongation and Torsade de Pointes

Cancer drug agents	Average QT Prolongation (ms)	Increase in QTc >60 ms (%)	QTc >500 ms (%)	Torsade de pointes (%)
Anthracyclines				
Doxorubicin	14	11-14	NA	NA
Histone deacetylase inhibitors				
Depsipeptide	14	20-23.8	NA	NA
Vorinostat	<10	2.7-6	<1	NA
Tyrosine kinase inhibitors				
Axitinib	<10	NA	NA	NA
Bosutinib	NA	0.34	0.2	NA
Cabozantinib	10-15	NA	NA	NA
Crizotinib	9-13	3.5	1.3	NA
Dasatinib	3-13	0.6-3	<1.4	NA
Lapatinib	6-13	11	6.1	NA
Nilotinib	5-15	1.9-4.7	<1.2	NA
Pazopanib	NA	NA	2	<0.3
Ponatinib	<10	NA	NA	NA
Sorafenib	8-13	NA	NA	NA
Sunitinib	9.6-15.4	1-4	0.5	<0.1
Vandetanib	36	12-15	4.3-8	Described, % NA
Vemurafenib	13-15	1.6	1.6	Described, % NA
Others				
Arsenic trioxide	35.4	35	25-60	2.5

Risk factors for QT prolongation in cancer patients

Risk factors	
Correctable	Non-correctable
Electrolyte imbalance • Nausea and emesis • Diarrhoea • Treatment with loop diuretics • Hypokalaemia (≤ 3.5 mEq/L) • Hypomagnesaemia (≤ 1.6 mg/dL) • Hypocalcaemia (≤ 8.5 mg/dL) Hypothyroidism	• Family history of sudden death (occult congenital LQTS or genetic polymorphisms) • Personal history of syncope • Baseline QTc interval prolongation • Female gender • Advanced age • Heart disease • Myocardial infarction • Impaired renal function • Impaired hepatic drug metabolism
Concurrent use of QT-prolonging drugs • Antiarrhythmic • Anti-infective • Antibiotic • Antifungal • Psychotropic • Antidepressant • Antipsychotic • Antiemetic • Antihistamine	

Clinical factors associated with increased risk of cancer-associated venous thromboembolism

Cancer-related factors

- Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma)
- Histology (specially adenocarcinoma)
- Advanced stage (metastatic)
- Initial period after cancer diagnosis

Patient-related factors

- Demographics: older age, female sex, African ethnicity
- Comorbidities (infection, chronic kidney disease, pulmonary disease, atherothrombotic disease, obesity)
- History of venous thromboembolism, inherited thrombophilia
- Low performance status

Treatment-related factors

- Major surgery
- Hospitalization
- Chemotherapy and anti-angiogenic agents
- Hormonal therapy
- Transfusions
- Central venous catheters

Modified from Khorana et al.

Strategies for surveillance and management of drug-induced pulmonary hypertension

Baseline assessment	• Consider risk factors and associated conditions for PAH • Assess NYHA/WHO functional class • Consider 6-minute walk test • Consider NT-proBNP • Assess echocardiographic level of probability of PH
Surveillance strategy	Asymptomatic • Assess NYHA/WHO functional class every 3 months • Assess echocardiographic level of PAP every 3 months • Consider presence of other indications for right heart catheterization • Consider further evaluation for suspected PH Symptomatic • Assess NYHA/WHO functional class • Perform 6-minute walk test • Sample blood for NT-proBNP • Assess echocardiographic level of probability of PH • Consider indications for right heart catheterization in PH referral centre • Consider interruption of cancer therapy

Strategies to reduce chemotherapy-induced cardiotoxicity

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy drugs	Identify and treat cardiovascular risk factors
	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities
	Minimize cardiac irradiation
Anthracyclines and analogues	Limit cumulative dose (mg/m ²): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	β-blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	β-blockers

Summarizes the potential benefits of exercise during and/or after cancer treatment

Improvement of:

- Cardiorespiratory and cardiovascular function
- Body composition (preservation or increase in muscle mass, loss of fat mass)
- Immune function
- Chemotherapy completion rates
- Muscle strength and flexibility
- Body image, self-esteem and mood

Reduction in:

- Number and severity of side effects including nausea, fatigue and pain
- Reduction of hospitalization duration
- Reduction of stress, depression and anxiety

Most recent reviews and meta-analyses on the incidence of hypertension with major VEGF inhibitor treatment

Drug	Number of studies included	Number of patients	Incidence of all grades of HTN, %	Incidence of stage 3-4HTN, %
Bevacizumab	20	6754	23.6	7.9
Sunitinib	13	4999	21.6	6.8
Sorafenib	13	2492	15.3	4.4
Axitinib	10	1908	40.1	13.1
Vandetanib	11	3154	24.2	6.8
Regorafenib	5	750	44.4	12.5

**Bevacizumab:
HBP and efficacy are correlated!
(Ann Oncol 2008)**

	Without severe HBP	Severe induced HBP
Patients (%)	80%	20%
Partial remission	20%	75%
Progression free survival (Months)	3.1	14.5

Sunitinib: 75 pts phase 1 and 2 trials (Chu, Lancet 2007, 370: 2011)

- **Cardiovascular events: 11.3% pts**
 - **AMI: 2**
 - **CHF:6**
- **Asymptomatic LV dysfunction: 28% pts**
- **Mean FE: from 64.5% to 54.9%**
- **High blood pressure: 47%**

**« Two types of chemotherapy-induced
LV dysfunction » (Ewer, JCO 2005, 23: 2900)
(« *concept probablement aussi séduisant qu'erroné* »)**

	Type 1: damage	Type 2: dysfunction	
drug	doxorubicin	trastuzumab	
evolution	Continuous	transient 3 months	
Dose-effect	cumulating	no	
mechanism	ROS, apoptosis,	ErbB2 inhibition	
ultrastructure	Damage +	No lesions	
relapse	certain	unprobable	

Sunitinib post-marketing studies: reversibility?

Khakoo (uncomplete)

- 2.7% CHF
- Delay: 22 days

Telli: 7/48

Schmidinger: 86 pts (all)

- 40% ECG changes
- 18% EF decline
- 9% symptomatic (ICU)

Chu (5/6, relapse)

	Patients	CV events	%
CAD +	4	3	75%
CAD -	71	5	7%

7-fold increase in cardiomyocyte apoptosis in pts with HBP



2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: - 3D-based LVEF - 2D Simpson's LVEF - GLS	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.