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The biological bases of treatment related cardiac and lung toxicity

Monica Mangoni

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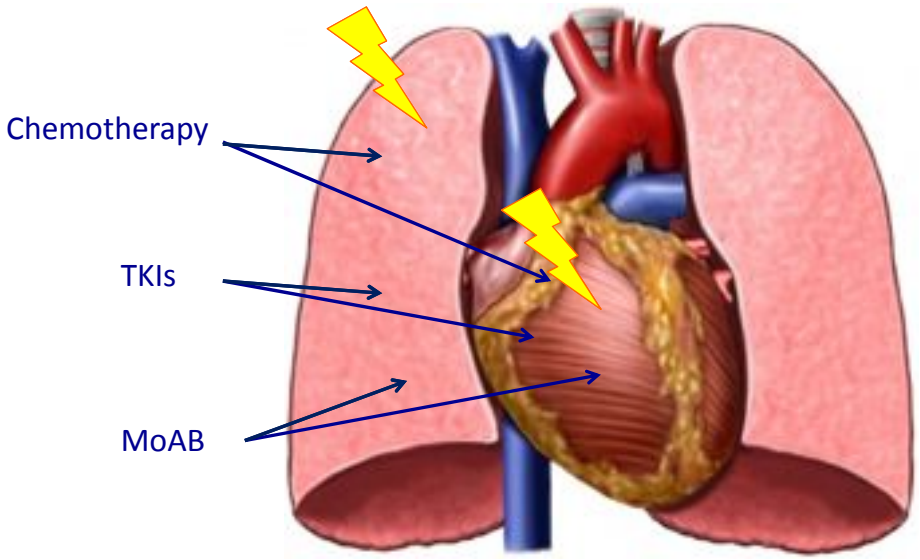
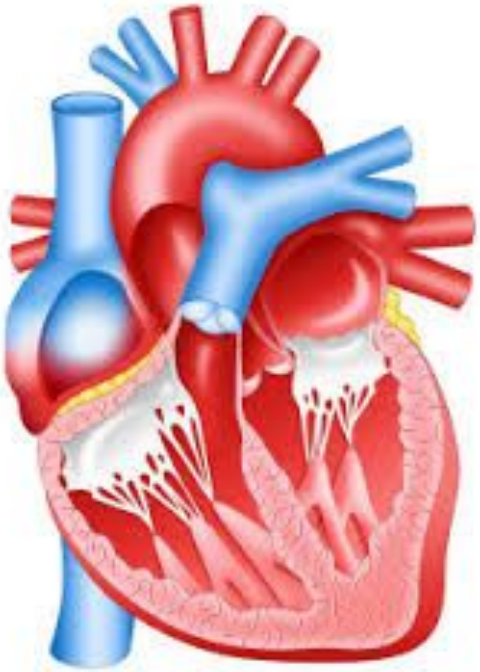
Cardiopulmonary toxicity of anticancer treatments





CARDIAC TOXICITY

Radiation effect

----------Early onset complications---

Acute pericarditis	during or soon after RT

----------Late complications----------

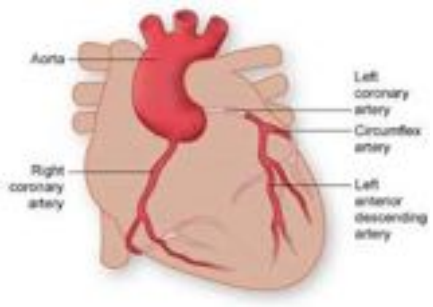
Chronic constrictive pericarditis	1-2 years
Myocarditis	follows chronic pericarditis
Coronary disease/atherosclerosis	> 5 years
Valvulopathy	> 5 years
Conduction deficits	> 5 years
Cardiomyopathy	> 5 years

Radiation-induced heart disease

Clinical manifestations of radiation-induced heart disease.

1. Radiation-induced pericarditis may occur if a large proportion of the heart (>30%) receives a dose of >50 Gy. The mean latency is approximately 1 year
2. Radiation-induced myocardial damage may be diagnosed at lower mean doses to the heart. The mean latency is >5 years
3. The risk of radiation-induced cardiovascular disease begins to increase 10 years after irradiation and is progressive with time. A significant increase of risk of cardiovascular disease has been observed after mean heart doses lower than 10% of the generally accepted tolerance dose to the heart of 40–50 Gy fractionated exposure

α/β <3
serial model



QUANTEC	
Breast cancer	V25<10%
HD+ chemotherapy	Whole heart doses >=15Gy
Pericarditis	Mean PD<26Gy V30<46%

Increased risk: by 7.4% per Gray MHD

Andratschke N, Radiother Oncol 2011; 100: 160-166
Gagliardi G, IJROBP 2010; 76: S77-S85
Darby SC,N Engl J Med 2013;368:987-98

Mechanism of damage

VASCULAR INJURY → **ISCHEMIA** → **FIBROSIS**

↓

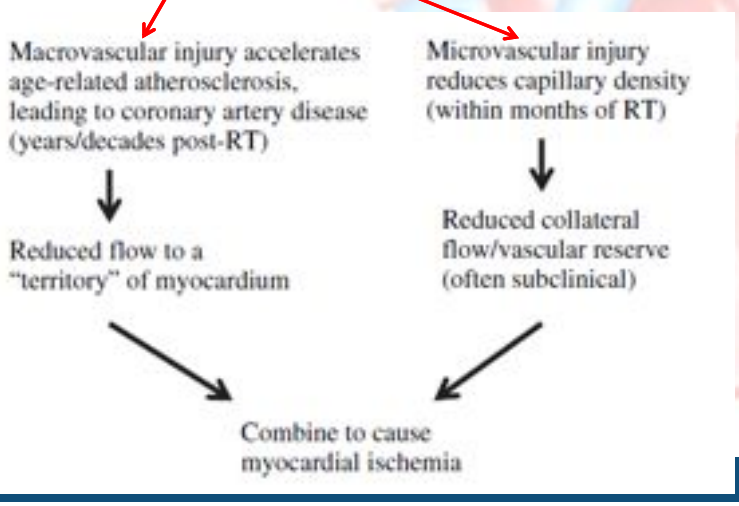
DIASTOLIC AND SYSTOLIC DYSFUNCTION

HEART FAILURE

Andratschke N, Radiother Oncol 2011; 100: 160-6

Mechanism of damage

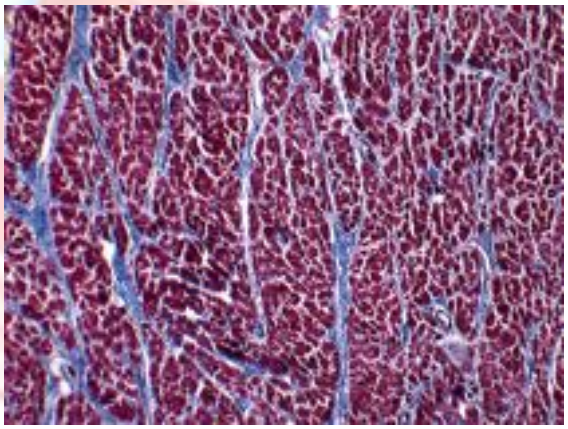
VASCULAR INJURY → **ISCHEMIA** → **FIBROSIS**



Darby SC, IJROBP 2010; 76: 656-65

Mechanism of damage

VASCULAR INJURY → **ISCHEMIA** → **FIBROSIS**



Mechanism of damage

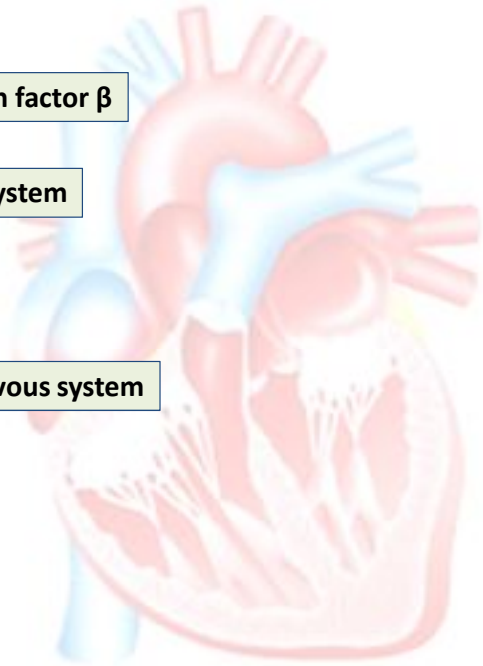
VASCULAR INJURY → **ISCHEMIA** → **FIBROSIS** → DIASTOLIC AND SYSTOLIC DYSFUNCTION → **HEART FAILURE**

↑beta-adrenoceptors
by 50%
in the irradiated heart
already 2 months after IR

Schultz-Hector S, Radiat Res 1992; 129: 281-9

Andratschke N, Radiother Oncol 2011; 100: 160-6

Main actors in response to radiation



- **Transforming growth factor β**
- **Renin-angiotensin system**
- **Mast cells**
- **Cardiac sensory nervous system**
- **Endothelin system**

Chemotherapy: cardiac effects

5 categories

1. direct cytotoxic effects (cardiac systolic dysfunction)
   - Anthracyclines
   - moAbs
   - TKIs
   - Alkylating agents
   - IFNα
2. cardiac ischemia
   - 5-FU
   - Topoisomerase inhibitors
   - Antitumor antibiotics
3. arrhythmias (++ torsade de pointes -QTprolonging drugs)
   - Anthracyclines
   - Targeted therapies
4. pericarditis
   - Cyclophosphamide
   - Cytarabine
   - Bleomycin
5. repolarisation abnormalities
   - Anthracyclines

Berardi R. Critical Reviews in Oncology/Hematology 88 (2013) 75–86

Anthracyclines

Cardiac myocyte injury

- Oxidative stress
- Anthracyclines compounds intercalate into nucleic acid
- Interaction with topisomerase
- Mitochondrial dysfunction→ alteration ATP→ contractile dysfunction
- Degradation of myofilaments, desmin and titin (disruption of sarcomeres)
- Impair calcium handling
- Alter drug efflux pumps
- Reduce cardiac progenitor cells

Geisberg C, Curr Heart Fail Rep 2012; 9: 211-218

ErbB2-targeted therapies

- Inhibit prosurvival intracellular signaling
- Augment anthracycline-induced myofilament disarray
- Impairmenty of contractility
- Inhibit ErbB-regulated angiogenesis
- Produce antibody-directed cellular cytotoxicity (moAb ErbB2-targeted therapies)

Geisberg C, Curr Heart Fail Rep 2012; 9: 211-218

Angiogenesis inhibitors

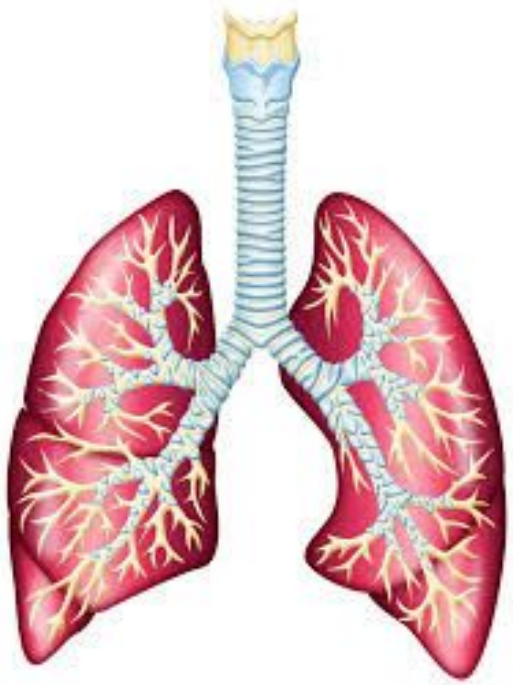
Hypertension: ↓NO syntesis

VEGF-targeted therapies: Inhibit cardiovascular repair and vascular growth

Therapies that inhibit PDGFR: Impair response to pressure overload

Inhibition of 5' adenosine monophosphate-activated protein kinase (AMPK)**:** Disrupt metabolic response to ischemic injury

Geisberg C, Curr Heart Fail Rep 2012; 9: 211-218



PULMONARY TOXICITY

Radiation-induced lung disease

----------Acute/subacute toxicity------

Radiation pneumonitis 4-12 weeks

----------Chronic toxicity----------

Radiation-induced fibrosis 6 months to 2 years

irradiated volume

absorbed dose

number of fractions

dose per fraction

dose rate

chemotherapy

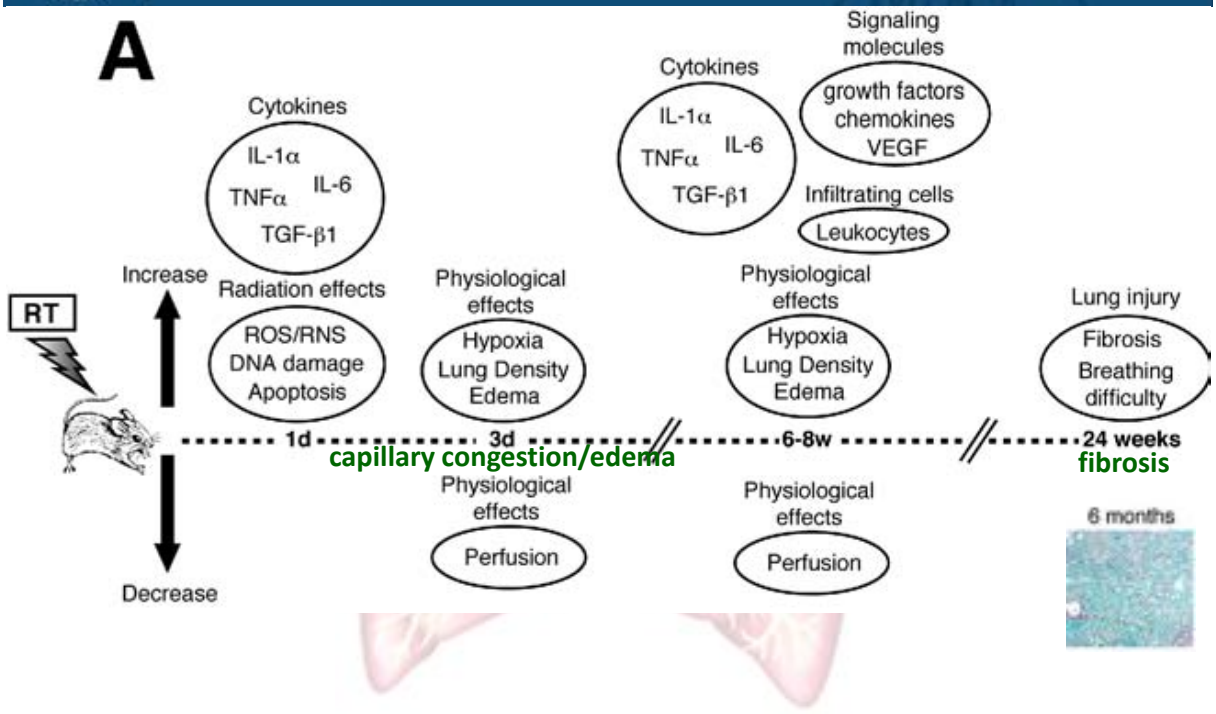
genetic factors

pre-existing lung disease

QUANTEC	
V20 30-35%	To limit the risk of RP<=20–23 Gy
MLD <=20–23 Gy	

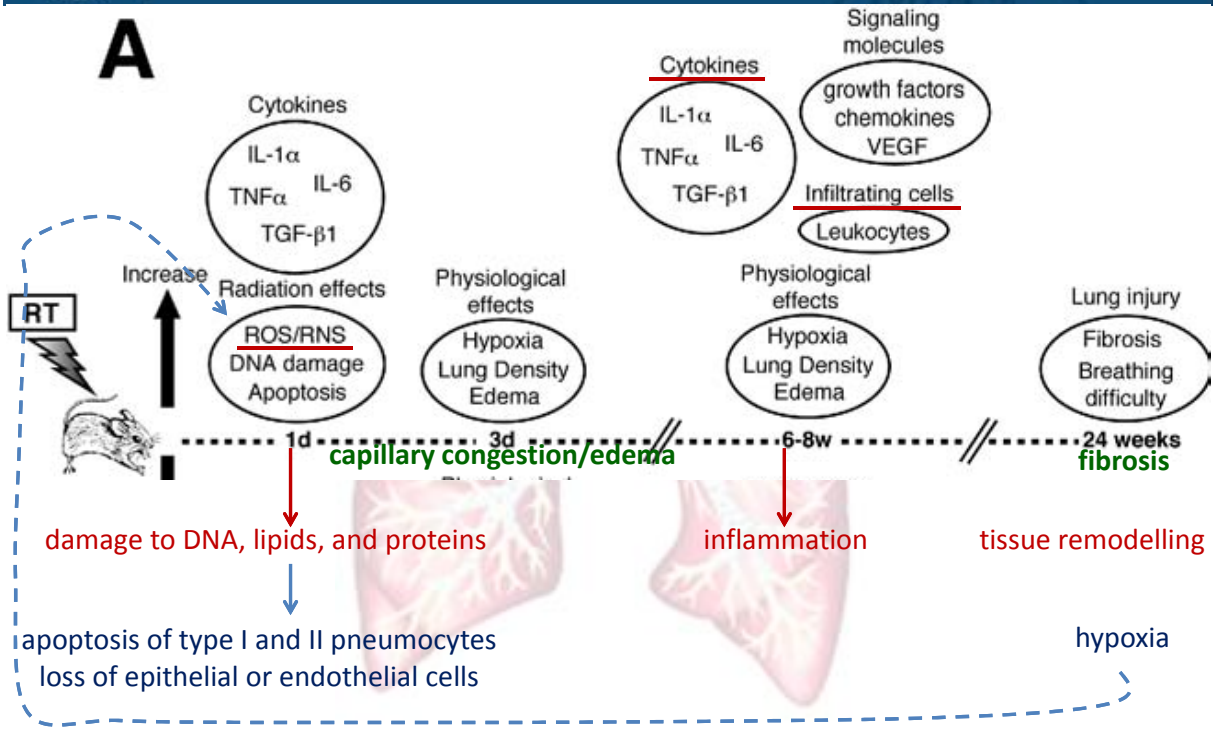
Ding NH. Current Drug Targets 2013; 14: 1347-56

Mechanisms of damage



Graves PR. Semin Radiat Oncol 2010; 20:201-207

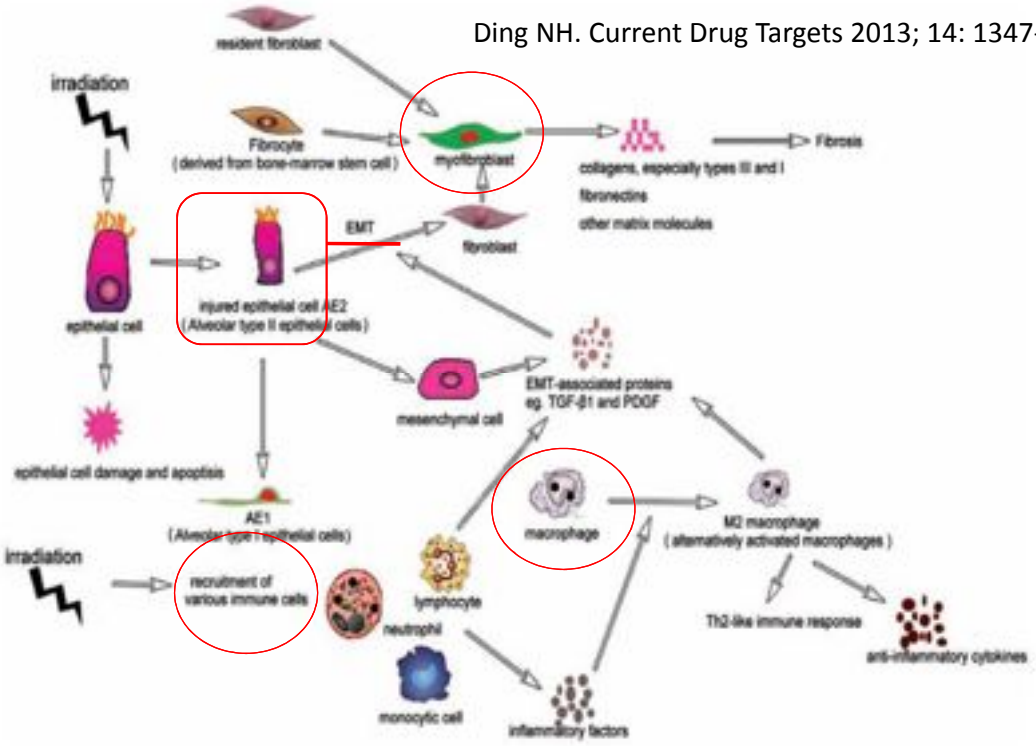
Mechanisms of damage



Graves PR. Semin Radiat Oncol 2010; 20:201-207

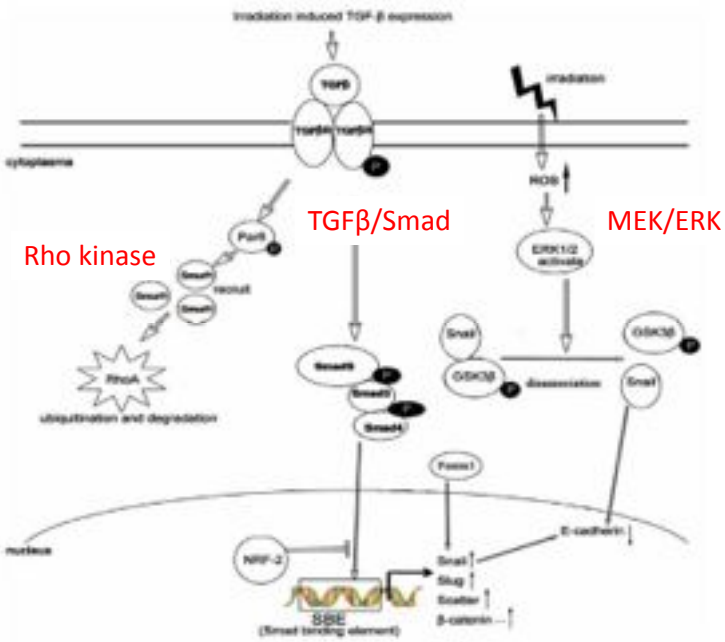
Cells involved in RILF

Ding NH. Current Drug Targets 2013; 14: 1347-56



Cytokines and related factors

- Transforming growth factor β
- ECM: vimentin, α-SMA, E-cadherin, Snail MMPs, TIMPs
- NF-κB network: TNFα, IkB, JNK
- M-CSF and MCP-1
- Th1 and Th2 cytokines
- ROS
- Additional signaling pathways



Ding NH. Current Drug Targets 2013; 14: 1347-56

Chemotherapy-induced pulmonary injury

pulmonary edema-diffuse alveolar damage- interstitial pneumonia-pulmonary haemorrage- fibrosis

Table 1. Selected mechanisms of chemotherapy-induced injury and pathologic findings

	Pathology	Proposed mechanisms
Cytotoxic agents		
Bleomycin	Endothelial blebbing, interstitial edema, type I pneumocyte necrosis with metaplasia of type II cells	Direct oxidative effects, leukocyte influx, release of proteases
	Polymorphoneutrophil infiltration, fibroblast proliferation	
	Eosinophilic infiltration (occasional)	Increased collagen synthesis
Mitomycin	Similar to bleomycin	Direct oxidative effects
Alkylating agents		
Cyclophosphamide	Endothelial swelling, dysplasia of pneumocytes	Reactive oxidative moieties
	Lymphocytic and histiocytic infiltrate	
	Interstitial fibrosis	
Busulphan	Pneumocyte dysplasia with type II cell atypical hyperplasia and atypical bronchial cells	Direct toxic effect
	Mononuclear infiltrate	
Antimetabolites		
Methotrexate	Lymphocyte, eosinophil, and plasma cell infiltration; noncaseating granulomata; rare fibrosis	Hypersensitivity or direct toxic effects
Cytosine arabinoside	Interstitial and alveolar edema without inflammation	Unknown
Nitrosoureas		
Carmustine	Predominately interstitial fibrosis, compare to bleomycin	Oxidant effects
Miscellaneous		
Procarbazine	Mononuclear cell infiltration with scattered eosinophilic foci	Hypersensitivity
Vinca alkaloids	Dysplasia of alveolar lining cells, interstitial and alveolar inflammatory cell influx, fibrosis	Unknown

Data from McKibben [1•].

Abid SH. Curr Opin Oncol 2001, 13:242–248

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Abid SH. Curr Opin Oncol 2001, 13:242–248

Chemotherapy associated lung injury

Cellular and apoptotic dysfunction

Impaired cell and tissue repair

(EGF signaling and angiogenesis)

Charpidou AG. Anticancer Research 2009; 29: 631-640

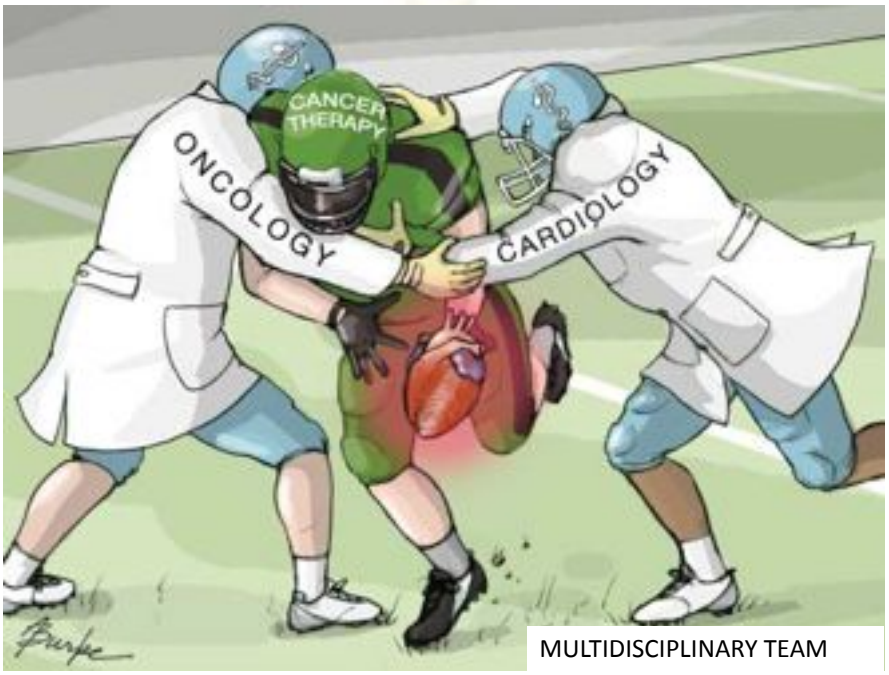
tyrosine kinase inhibitors

interstitial lung disease

- Chronic inflammation
- Inappropriate regeneration of the injured epithelium
- Apoptosis of type I and II pneumocytes
- Impaired repair (EGFR)

Min JH, Cancer Chemother Pharmacol (2011) 68:1099–1109

Specific care plan for each patient



MULTIDISCIPLINARY TEAM

JAMA, March 17, 2010—Vol 303, No. 11