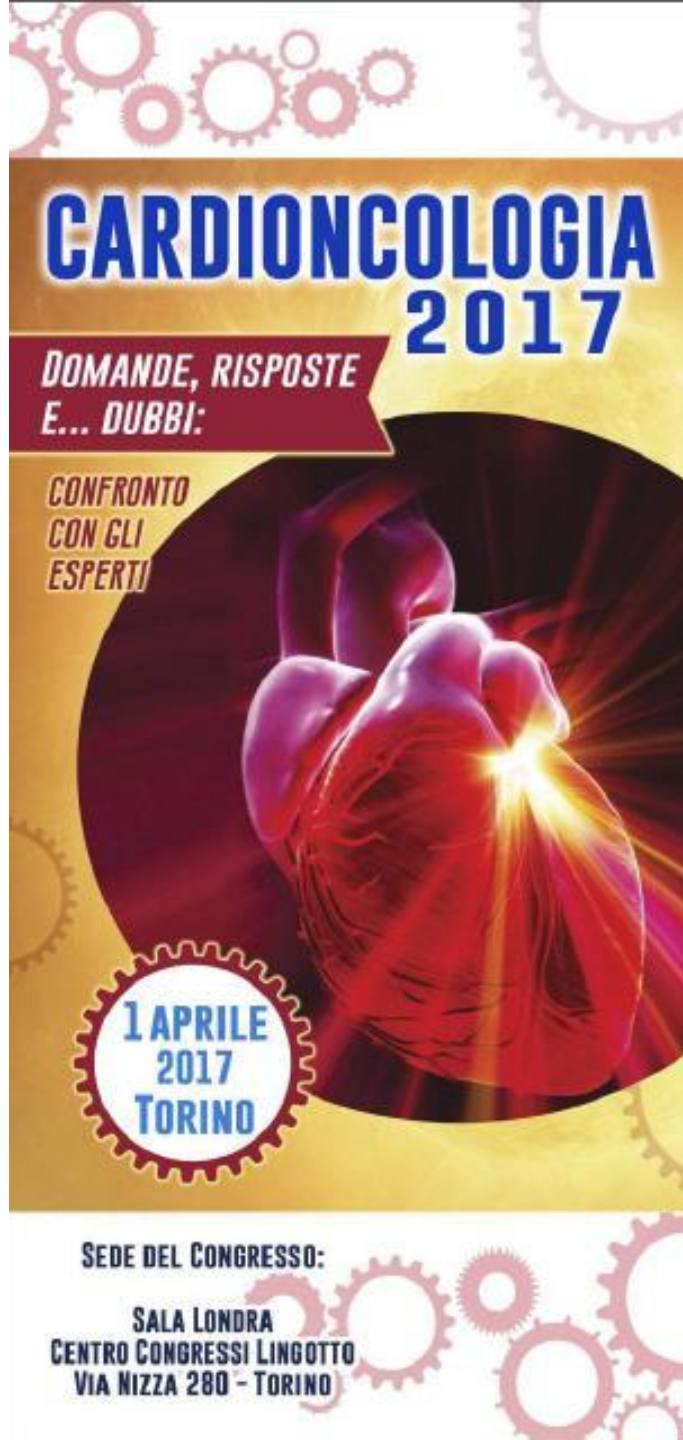




CARDIOTOSSICITA' ED ARITMIE

Il parere del cardiologo

Dr.ssa Iris Parrini
Ospedale Mauriziano di Torino

Quali terapie oncologiche possono determinare bradicardia, blocchi AV o disfunzione del nodo senoatriale ?

Main type of cardiac arrhythmias induced by chemotherapy drugs

Sinus bradycardia

Amsacrine, arsenic trioxide, bortezomib, capecitabine, cisplatin, combretastatin, crizotinib, cyclophosphamide, cytarabine, daunorubicin, fludarabine, 5-FU, mitoxantrone, paclitaxel, ponatinib, rituximab, taxanes, thalidomide, vinca alkaloids, vorinostat

- **AV block** Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, daunorubicin, doxorubicin, epirubicin, 5-FU, ifosfamide, IL-2, interferon- α , mitoxantrone, ponatinib, rituximab, taxanes, thalidomide
- **Intraventricular conduction block** Cisplatin, 5-FU, imatinib, paclitaxel, trastuzumab
- **Sinus tachycardia** Arsenic trioxide, bortezomib, bosutinib, capecitabine, carmustine, cyclophosphamide, epirubicin, 5-FU, paclitaxel, romidepsin, vorinostat
- **Atrial fibrillation** Alemtuzumab, amsacrine, bortezomib, cetuximab, cisplatin, cyclophosphamide, doxorubicin, gemcitabine, ifosfamide, IL-2, interferon- α , melphalan, ponatinib, rituximab, sorafenib, sunitinib, taxanes, vinca alkaloids
- **Supraventricular tachycardias** Amsacrine, capecitabine, cisplatin, cyclophosphamide, daunorubicin, doxorubicin, ifosfamide, interferon- α , IL-2, melphalan, ponatinib, taxanes
- **QT prolongation** Amsacrine, arsenic trioxide, bosutinib, cabozantinib, capecitabine, combretastatin, daunorubicin, doxorubicin, enzastaurin, eribulin mesilate, HDAC inhibitors (dacinostat, panobinostat, romidepsin, vorinostat), rituximab, small-molecule PKI (dasatinib, lapatinib, nilotinib, ponatinib, sorafenib, sunitinib, vandetanib)
- **Ventricular tachycardia/ fibrillation** Alkylating agents (Cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine, methotrexate), anthracyclines (daunorubicin, doxorubicin), arsenic trioxide, dasatinib, HDAC inhibitors (panobinostat, romidepsin), interferon- α /- γ , IL-2, monoclonal antibodies (alemtuzumab, rituximab, trastuzumab), taxanes
- **Torsades de pointes** Arsenic trioxide, dacinostat, daunorubicin, HDAC inhibitors, vorinostat
- **SD Camsacrine**, arsenic trioxide, cabozantinib, capecitabine, doxorubicin, 5-FU, interferon- α , nilotinib, romidepsin, rituximab, 5-FU 5-fluorouracil, AV atrioventricular, HDAC histone deacetylase, IL-2 interleukin-2, PKI protein kinase inhibitor, SCD sudden cardiac death

Le aritmie possono anche essere indipendenti dal trattamento chemioterapico

Cause permanenti

- Età
- Infiltrazione da tumori cardiaci
- Ischemia
- Ipertensione intracranica

Cause transitorie

- Disturbi elettrolitici
- Ipotiroidismo
- Stimolazione vagale
- Terapie (Bbloccanti, Ca-antagonisti)

In questo caso clinico quali farmaci possono aver indotto la complicanza ?

CICLOFOSFAMIDE Può indurre bradicardie e blocchi AV, sick sinus syndrome, se utilizzata ad alte dosi

DOXORUBICINA Sono generalmente reversibili
descritti rari casi di disfunzione del nodo SA

Table 1. Chemotherapeutic drugs associated with bradyarrhythmia development.

Chemotherapeutic drug	Type of bradyarrhythmia
Doxorubicin	Second - third-degree AV blocks, sinus bradycardia
Mitoxantrone	Sinus bradycardia, first-degree AV block
Epirubicin, daunorubicin, idarubicin	Sinus arrest, AV blocks, sinus bradycardia
Cyclophosphamide at high doses	Second degree AV blocks, sinoatrial block
Cisplatin	Sinus bradycardia
Paclitaxel	Sinus bradycardia
5-Fluorouracil	Branch block, first-degree AV block, complete AV block leading to death first-degree AV block
	Sinus bradycardia
Capecitabine	Sinus arrest
	Sinus bradycardia
Cytosine arabinoside at intermediate and high doses	Sinoatrial block, AV blocks
Fludarabine	Sinus bradycardia
	Sinus bradycardia

Antineoplastic drug-induced bradyarrhythmias

Carla Minoia[†], Margherita Giannoccaro, Angela Iacobazzi, Daniele Santini, Nicola Silvestris, Agnese Fioretti, Stefano Oliva & Attilio Guarini

[†]National Cancer Centre "Giovanni Paolo II", Department of Oncology, Haematology Unit, Bari, Italy

DrugSaf 2012

Table 3. Defined mechanisms of bradyarrhythmia induction by antineoplastic agents.

Antineoplastic agent	Pathogenetic mechanism for bradyarrhythmias	Ref.
Doxorubicin	Release of vasoactive molecules (e.g., histamine); histamine stimulates its receptors on central nervous system with decrease of sympathetic activity and consequent negative chronotropic effect Stimulation of parasympathetic system (nausea, emesis)	[1,8,9]
Mitoxantrone	Gradual, competitive beta-adrenergic blocking effect	[11]
Cyclophosphamide	Reversible damage of conduction system due to microangiopathy or transient coronary spasm during infusion Vagal stimulation	[25]
Cisplatin	Hypomagnesemia, hypocalcemia	[2,19,28]
Paclitaxel	Impairment of autonomic modulation of the heart rate Direct negative chronotropic effect Modifications of calcium signals on rat cardiomyocytes and consequent calcium oscillation, binding neuronal calcium sensor 1 (NCS-1) Interference with elimination of doxorubicin, its accumulation inside cardiac tissue and conversion to its cardiotoxic metabolite doxorubicinol	[2,31-33,36]
Cytosine arabinoside	DNA modifications on cardiomyocytes leading to apoptosis Loss of calcium ion regulation	[59,60]
Thalidomide	Reversible changing in autonomic balance through the inhibition of various cytokines, among all TNF-alfa, leading to an overactivation of the parasympathetic system with consequent bradycardia	[67,69]
Bortezomib	Desensitization of adrenergic receptors Reduced myocardial cytoprotection Cardiomyocyte apoptosis Mitochondria damage	[85,87,88]

Antineoplastic drug-induced bradyarrhythmias

Carla Minoia[†], Margherita Giannoccaro, Angela Iacobazzi, Daniele Santini, Nicola Silvestris, Agnese Fioretti, Stefano Oliva & Attilio Guarini

[†]National Cancer Centre "Giovanni Paolo II", Department of Oncology, Haematology Unit, Bari, Italy

DrugSaf 2012



Come prevenire ?

- ECG a 12 derivazione
- storia personale e familiare di malattia cardiaca
- evitare farmaci che inducono bradicardia
- controllo elettroliti

THALIDOMIDE
(angiogenesis inhibitor)

- Ormoni tiroidei

PACLITAXEL
(anti-microtubule)

- se il paziente è bradicardico o presenta disturbi della conduzione di base, **monitoraggio ECG e pressione arteriosa durante le prime ore di infusione**
- consigliata premedicazione con corticosteroidi



Come trattare ?

THALIDOMIDE
(angiogenesis inhibitor)

- nessuna indicazione se il paziente è asintomatico
- se i sintomi sono legati alla bradicardia, prendere in considerazione la riduzione della dose o l'interruzione della terapia
- nel mieloma responsivo indicazione a pacemaker se non ci sono alternative
indicazione a PM se BAV III

PACLITAXEL
(anti-microtubule)

interrompere la chemioterapia se compare BAV o se la bradicardia è emodinamicamente instabile

La radioterapia ad alte dosi
può determinare come effetto tardivo
un danno delle vie di conduzione?

si, sono eventi molto rari ma descritti in letteratura

Table 3 Risk Factors for Radiation-Induced Cardiotoxicity

Total dose >30–35 Gy
Higher dose/fraction >2 Gy/day
Field size (volume of heart irradiated)
Relative field weighting (anterior/posterior positioning)
Presence of tumor next to the heart
Younger age at exposure
Time since exposure
Type of radiation source (cobalt)
Cardiotoxic chemotherapy (e.g., anthracycline)
Other cardiovascular risk factors (e.g., diabetes, smoking)
Technique (reduced with CT plan)

Adapted, with permission, from Gaya et al. (16) and Carver et al. (20).

CT = computed tomography.

STATE-OF-THE-ART PAPER

Cardiac Complications of Thoracic Irradiation

Catherine Jaworski, MBBS,* Justin A. Mariani, MBBS, PHD,*yzx Greg Wheeler, MBBS,x

David M. Kaye, MBBS, PHD*yz JACC 2013

Conduction system. Abnormalities along the entire conduction system have been described in the setting of radiotherapy, including varying degrees of atrioventricular block, sick sinus syndrome, prolonged QTc, supraventricular arrhythmias, and ventricular tachycardia.

Right bundle branch block is more commonly observed than left bundle branch block post-RT, likely due to higher radiation exposure of the right ventricle due to its anterior location. Ventricular ectopy might occur in up to 50% of patients exposed to mediastinal irradiation, often secondary to ventricular fibrosis

STATE-OF-THE-ART PAPER

Cardiac Complications of Thoracic Irradiation

Catherine Jaworski, MBBS,* Justin A. Mariani, MBBS, PHD,*yzx Greg Wheeler, MBBS,x

David M. Kaye, MBBS, PHD*yz JACC 2013

GRAZIE PER L'ATTENZIONE

