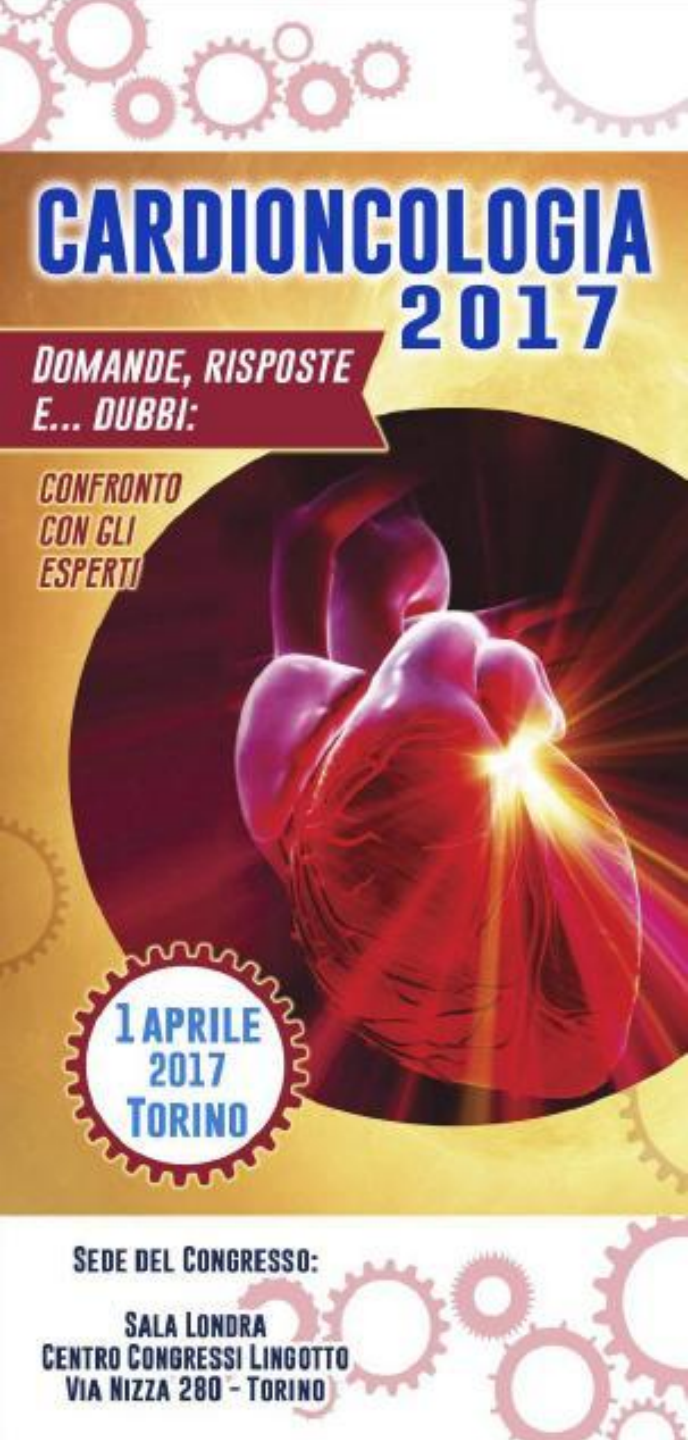


CARDIOTOSSICITA' ED ARITMIE

Il parere dell'ematologo

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Dr.ssa Carola Boccomini

SC Ematologia – Dr. U. Vitolo

AO Città della Salute e della Scienza

Torino, Italy

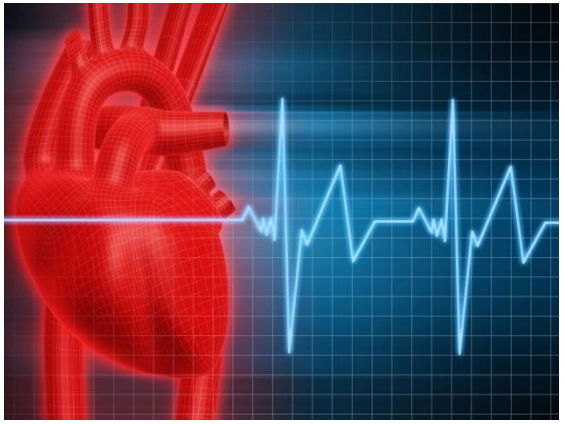
Why focusing on cardioncology?

- ✓ Cardiac injury is one of the most impairing side effects of anticancer treatment
- ✓ Recent extension of
  - ✓ improved surgical approaches
  - ✓ range of available drugs
  - ✓ use of combination regimens
  - ✓ use of concomitant radiation therapy
- ✓ Improved life expectancy
- ✓ Improved outcome of cancer patients

CARDIOVASCULAR DISEASE IS THE 2nd CAUSE OF LONG TERM MORBIDITY AND MORTALITY OF CANCER SURVIVORS

Minoia C, et al; Expert Opin Drug Saf 2012

Chemotherapy-induced arrhythmia



- ✓ The relationship between chemotherapy and arrhytmias is not well established
- ✓ Cancer itself creates an arrhytmogenic mileu
- ✓ More than one chemotherapeutic agent is used in each patients, either simultaneously or sequentially, making it difficult to decide which one caused this side effect

Guglin M, et al; Europace 2009

Chemotherapy-induced arrhythmia

	AF	Other type
Antracyclines	6-38%	
Vinca Alkaloids		25% (bradi)
Antimetabolites (Gemcitabine)	8%	
Alkylating agents: Cisplatin	4-6%	1-3% VT
Melphalan	6.6-11.8%	
Ifosfamide	n.s	n.s, PVC and VT
Rituximab	? reversible	

Guglin M, et al; Europace 2009

Antineoplastic drug-induced bradyarrhythmias

Cardiac rhythm disorder characterized by a reduction or loss of cardiac beats, often with a ventricular rate <60 bpm.

- Sinus bradycardia o arrhythmia
- Sinus node disfunction
- Atrio-ventricular conduction disorders

LESS FREQUENT THAN TACHYARRHYTMIAS AND MORE FAVORABLE ON PATIENT OUTCOME BUT UNDERESTIMATED

Minoia C, et al; Expert Opin Drug Saf 2012

Antineoplastic drug-induced bradyarrhythmias

PRE-EXISTING FACTORS

- ✓ Old age
- ✓ Paracardiac or cardiac localization
- ✓ Infiltrative conditions (amyloidosis, fibrosis or sclerosis)
- ✓ Cardiomyophaties
- ✓ Ischemic injuries
- ✓ Valvular pathologies

DIRECT DAMAGE

- ✓ Stimulation of parasympathetic system
- ✓ Beta-adrenergic blocking
- ✓ Release of vasoactive molecules

TRANSIENT CAUSES

- ✓ Electrolyte imbalance (hypoK, hypoMg)
- ✓ Metabolic alterations (Hypotiroidism)
- ✓ Vagal stimulation due to emesis, inflammation or trauma (surgery/catheterism)
- ✓ Drugs: Beta or Calcium-channel blockers, digoxin, amiodarone

Minoia C, et al; Expert Opin Drug Saf 2012

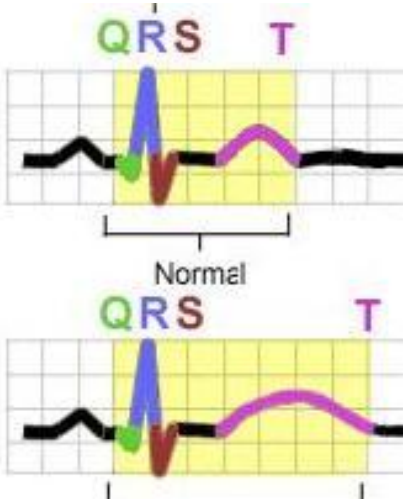
Antineoplastic drug-induced bradyarrhythmias

Drug
Antracyclines
Alkylating agents
Cyclophosphamide HD
Cisplatinum
Antimetabolites (Citarabine)
Fludarabine
Thalidomide
Bortezomib
Rituximab

Minoia C, et al; Expert Opin Drug Saf 2012

QT interval prolongation

- ✓ ↑QT interval represents the principal clinical surrogate marker to evaluate the torsadogenic risk of a drug
- ✓ Lack of standardized method of measurement, resulting in diminished specificity
- ✓ QT interval duration depends on heart rate
- ✓ Several formulas to mathematically correct QT (QTc): Bazzett, Fridericia, Framingham and Hodges formulas
- ✓Great controversy over normal parameters
- ✓ Ventricular arrhytmias, particularly TdP, are correlated with QTc>500 msec; however no established threshold below which ↑QT is considered free of proarrythmic risk



MECHANISM OF ACTION

- the three-dimensional structural configurations of these agents uniquely interact with HERG k+
- Indirect effect on HR

Locatelli M, et al; Targeted Oncology, 2015
Strevel EL, et al; JCO 2007

AGE

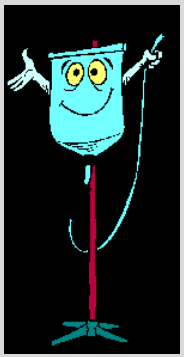
COMORBIDITIES

- ✓ Female gender
- ✓ Cardiovascular disease: bradycardia, mitral valve prolapsed, low EF, cardiac hypertrophy, myocarditis, AV blocks, ischemia
- ✓ Endocrine disorders: Hytoroidism
- ✓ Electrolyte disturbance: HypoK, HypoMg and HypoCalcemia
- ✓ Other disease: epatic or renal failure

CONCOMITANT MEDICATION

SIDE EFFECTS

- ✓ Nausea/vomiting
- ✓ Diarrhea
- ✓ Dicreased oral intake



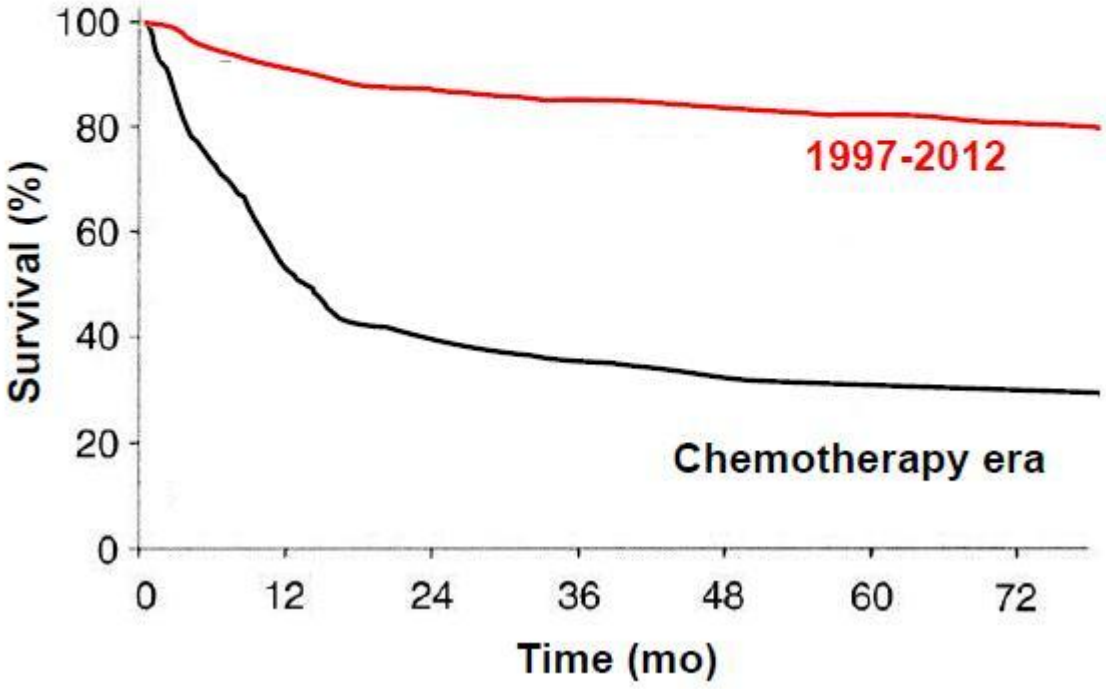
Locatelli M, et al; Targeted Oncology, 2015
Strevel EL, et al; JCO 2007

	DRUGS
Antiarrhythmics	Quinidine, Sotalol, Dysopiramide, Procainamide, Amiodarone, Verapamil
Psychotropics	Amitriptyline, Venlafaxine, Doxepin, Haloperidol, Risperidone, Olanzapine, Chlorpromazine , Quetiapine
Antimicrobials	Clarithromycin, Erythromicin, Azithromicyn, Chloroquine, Moxifloxacinn, Levofloxacin, Pentamidine, Foscarnet, Trimethoprim+Sulfamethoxazole
Antifungals	KetoKonazole, Miconazole, Voriconazole, Itraconazole
Antihistamines	Terfenadine, Cetirizine
Prokinetics	Cisapride, Domperidone
Antiemetics	Ondansetron, Granisetron, Metoclopramide

Locatelli M, et al; Targeted Oncology, 2015
Strevel EL, et al; JCO 2007

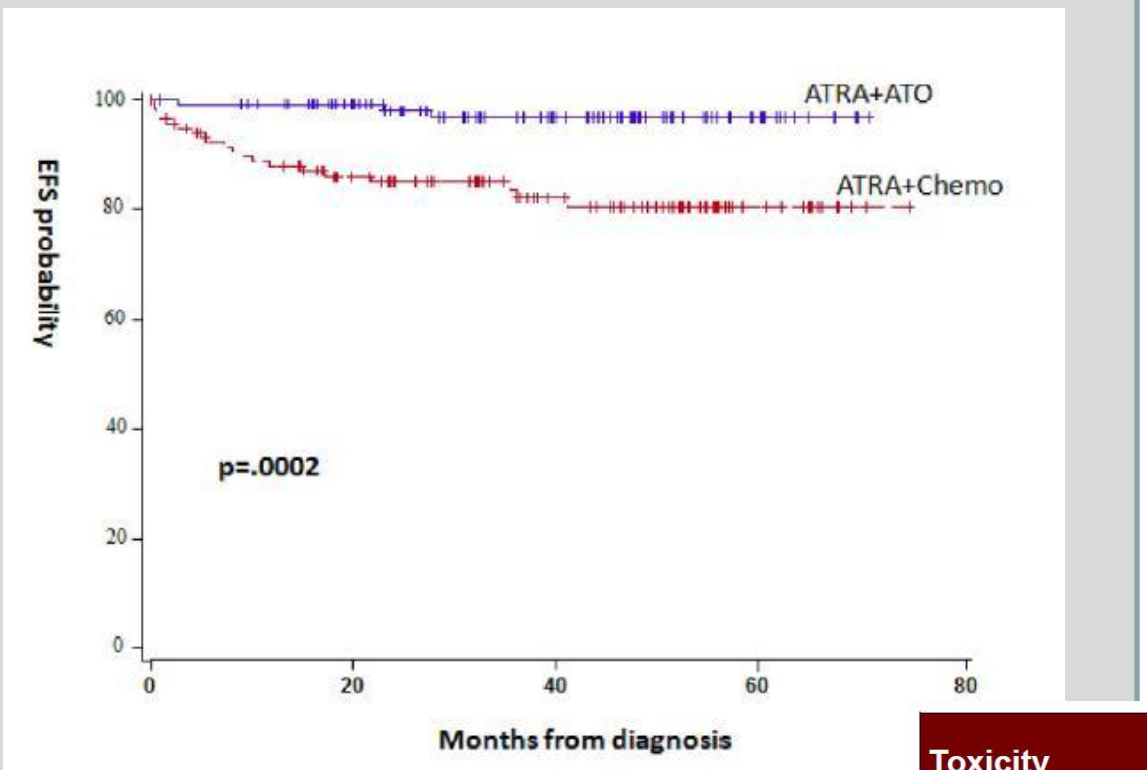
QT interval and Arsenic Trioxide

Reported outcomes for APL pre- and after ATRA



- ✓ Induction death
- ✓ Death in remission
- ✓ Toxicity of consolidation treatment
- ✓ Therapy related MDS/AML

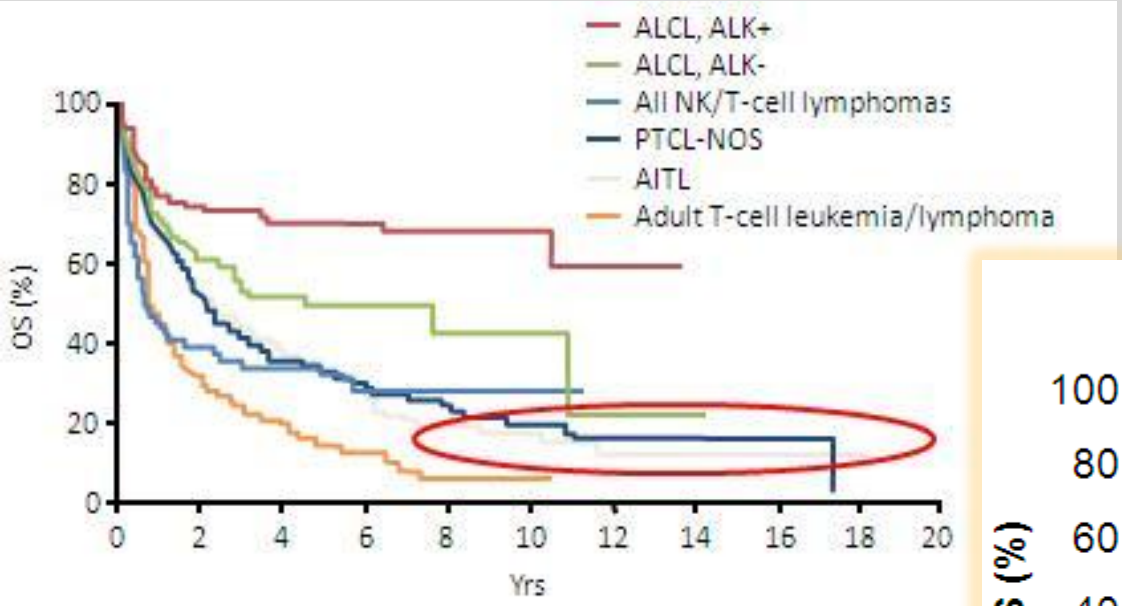
QT interval and Arsenic Trioxide

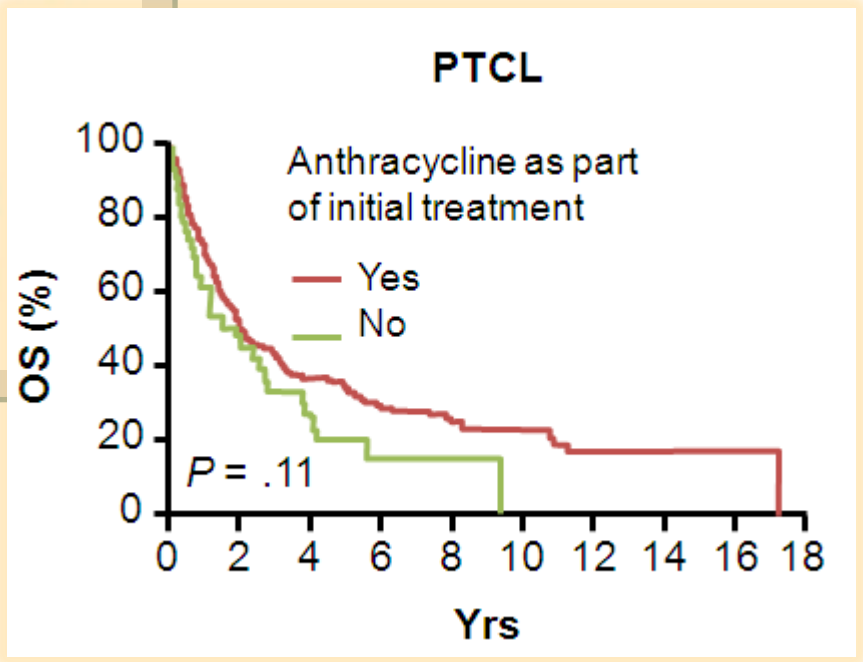


Toxicity	ATRA+ATO	ATRA+Chemo	P value
QTc prolongation[1], %	13	0	0.0005
Hepatic toxicity[1] (Grade 3-4), %	57	5	<0.0001
Leukocytosis[2] (>10x10^9/L), %	47	24	0.007

QT interval and Romidepsine

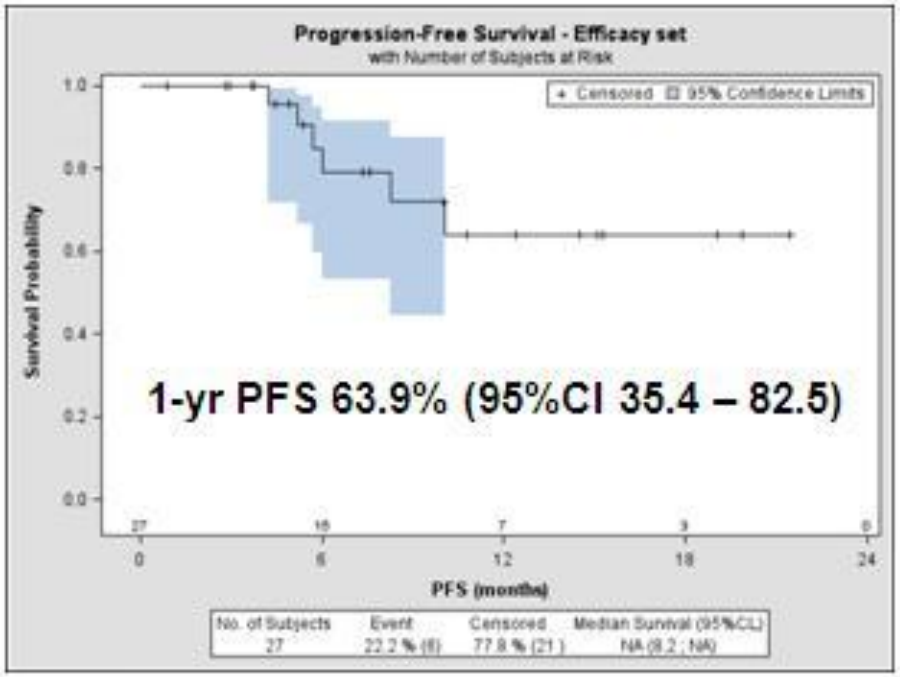
OS varies according to subtype
Median OS ranges from 1-3 yrs

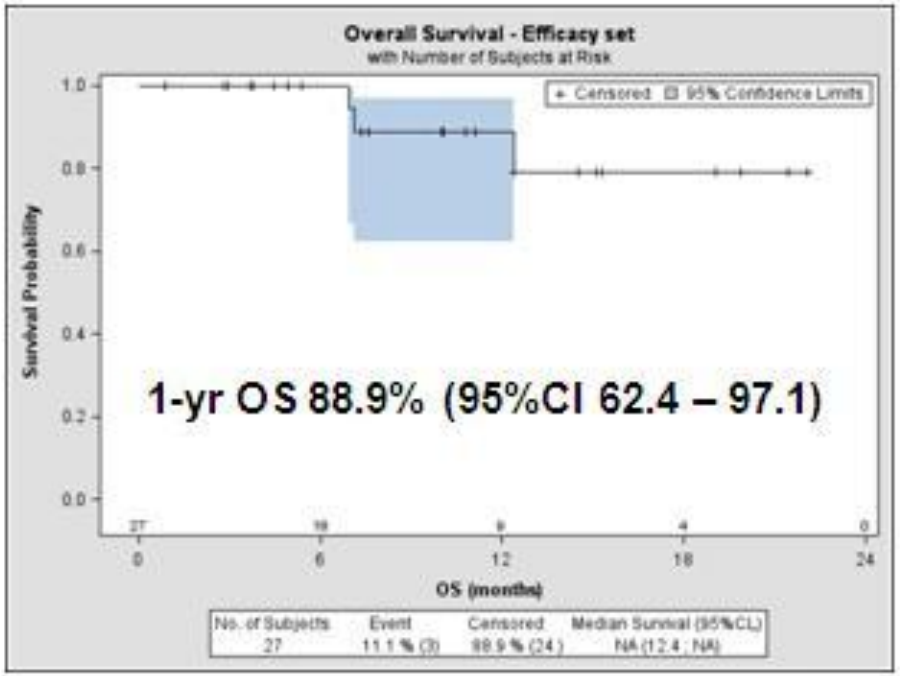




Vose J, et al. JCO, 2008

QT interval and Romidepsine





Romidepsin can be combined with CHOP at the price of foreseeable haematological toxicity. Some cardiovascular events have been observed but the relationship remains unclear. Efficacy results are promising.

Dupuis J, et al; Lugano 2013

Ibrutinib-related atrial fibrillation in patients with mantle cell lymphoma

Atrial fibrillation associated with ibrutinib in Waldenström macroglobulinemia

The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis

Atrial fibrillation in CLL patients treated with ibrutinib. An international retrospective study

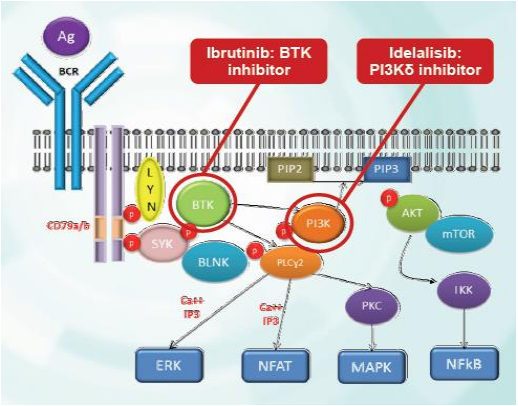
Proposed Algorithm for Managing Ibrutinib-Related Atrial Fibrillation

Additional data needed for a better understanding of the potential relationship between atrial fibrillation and ibrutinib

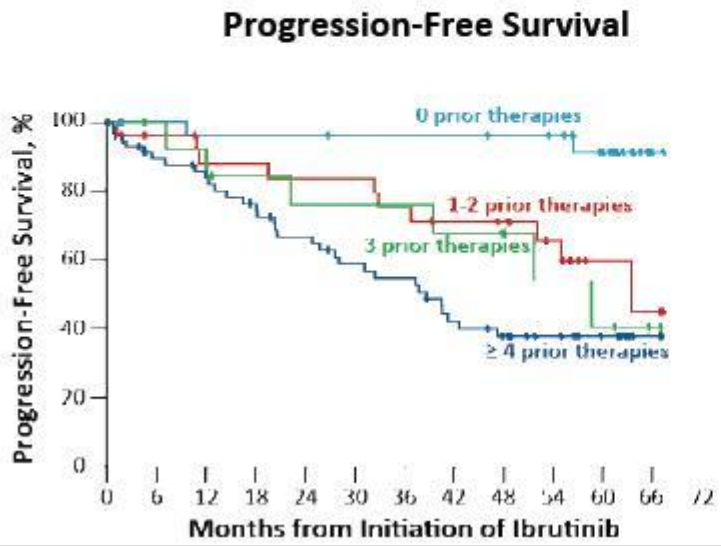
Atrial fibrillation, anticoagulant stroke prophylaxis and bleeding risk with ibrutinib therapy for chronic lymphocytic leukaemia and lymphoproliferative disorders

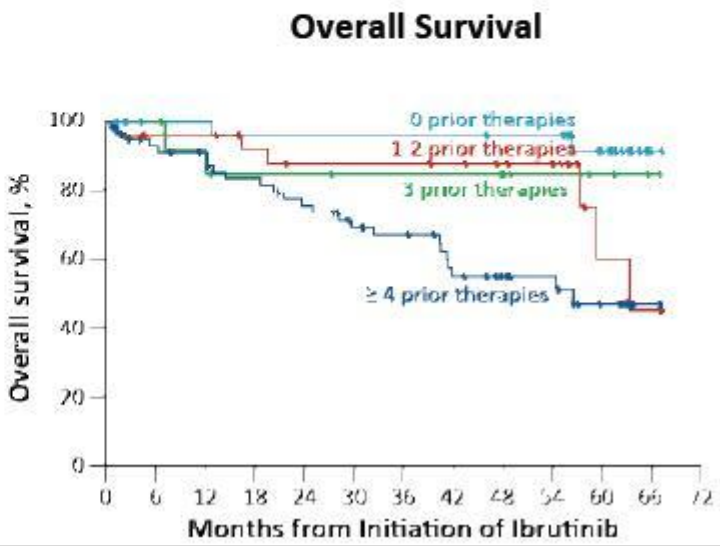
Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling

The BTKi IBRUTINIB is the new standard of care in untreated del17p or p53 mutated B-LLC or relapsed/refractory B-LLC and MCL and in Waldenstrom Macroglobulinemia.



Ibrutinib Survival by Number of Lines of Prior Therapies





Ibrutinib–Related Atrial Fibrillation (IRAF)

✓ Reported IRAF incidence of 3.5-7.7%, significantly higher than alternative therapies (0.5-2.4%) or general population

✓ Median time of onset 3.8 months with >80% of AF events occurring in the first 6 months.

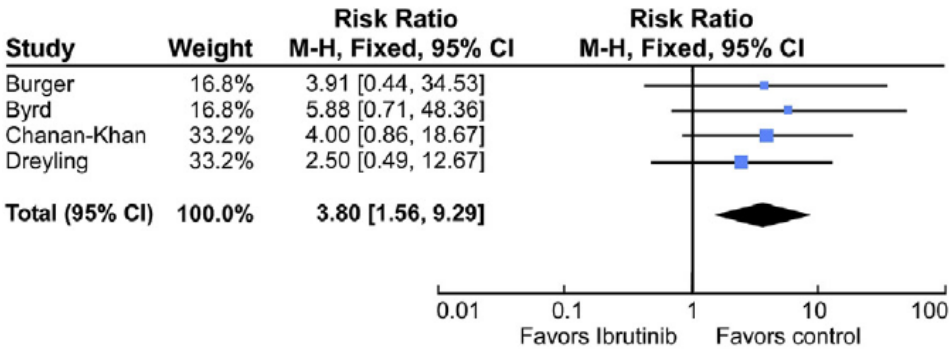
UNCLEAR MECHANISM OF ACTION

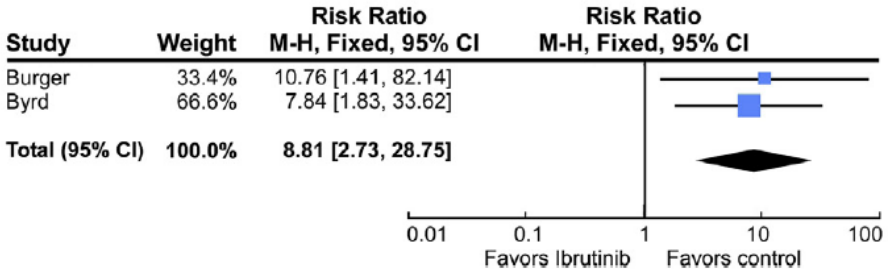
- Both BTK and TEC transcripts were expressed in human heart tissue and were is a higher expression in atrial tissue in AF condition than synus rhytm
- BTK and TEC regulate the PI3k-AKT pathway, thas is a critical regulator of cardiac protection under stress condition
- Ibrutinib significantly reduced PI3k-AKT activity in cardiac cells
- Inhibition of BTK and TEC kinases, that leads to decreased PI3k-AKT signalling, is one potential explanation of IRAF

McMullen JR, et al; Blood, 2014
Thompson PA, et al; BJH, 2016

Risk of Atrial Fibrillation and Bleeding Diathesis Associated With Ibrutinib Treatment: A Systematic Review and Pooled Analysis of Four Randomized Controlled Trials

- ✓ Ibrutinib treatment was associated with a significantly higher risk of serious AF/AFL: RR 3.80
- ✓ Ibrutinib treatment was associated with a significantly higher risk of all-grade AF/AFL: RR 8.81
- ✓ The risk of these adverse events was not different between subgroups (pathology, treatment setting, dose and duration of Ibrutinib exposure)

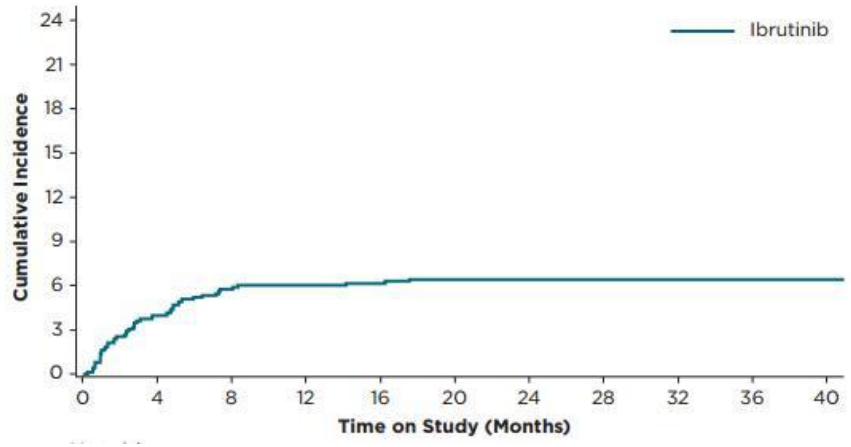


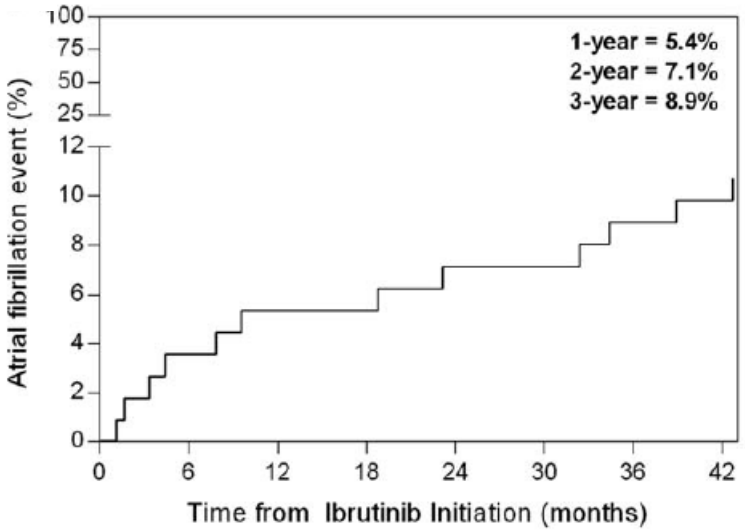


Yun S, et al; Clinical Lymphoma, Myeloma & Leukemia, 2017

Ibrutinib–Related Atrial Fibrillation (IRAF)

- ✓ Patients with known history of AF experienced events earlier than those without history of AF
- ✓ **Discordant data:** curve plateaus beginning at 8 months and does not rise above 7% vs incidence may continue to increase up to 16% in longer-follow-up (up to 26 months)
- ✓ **Unclear if late AF depends on increased propensity in prolonged Ibrutinib exposure or higher risk due to advancing age, hypertension, prolonged disease history and effects of prior therapies**
- ✓ **It would be useful to know if occurence of AF is ibrutinib dose-dependent or an idiosyncratlc response**





Gustine JN, et al; AJH, 2016

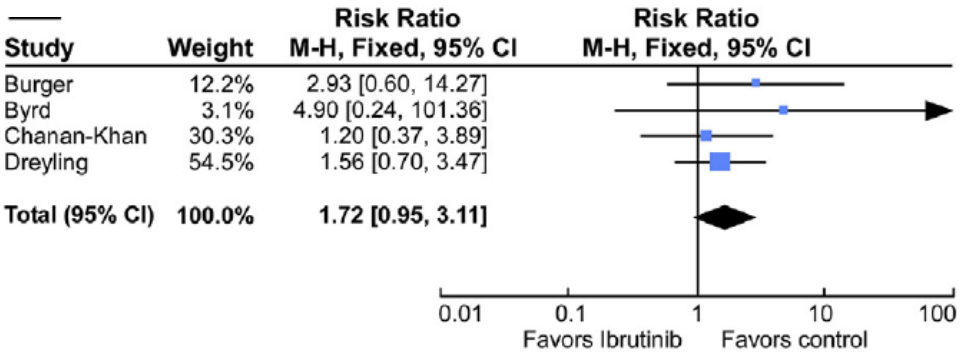
Ibrutinib and Bleeding risk

✓ In Ibrutinib-treated patients, anticoagulant choice is complicated by the known increased bleeding risk

✓ Usually presenting as cutaneous bruising or minor bleeding

✓ Ibrutinib treatment was associated with a significantly higher risk of all-grade bleeding: RR 2.93 while there was no difference in major bleeding rates: RR 1.72

✓ Impact of cuncurrent use of antiplatelet agents (commonly used in cardiovascular disases) needs future study



UNCLEAR MECHANISM OF ACTION

- Anti-platelet effects
- It inhibits platelet adesion to collagen and to von Willebrand factor
- It inhibits collagen mediated platelet aggregation

Yun S, et al; Clinical Lymphoma, Myeloma & Leukemia, 2017

Drugs interactions: Ibrutinib, anti-arrhythmic and anti-coagulant

- ✓ Ibrutinib is metabolized by CYP3A: Diltiazem and Verapamil are moderate inhibitors
- ✓ Ibrutinib inhibits P-glycoprotein and thus may increase exposure to P-glycoprotein substrates: Digoxin and Amiodarone, Dabigatran

- ✓Through CYP3A: Apixaban and Rivaroxaban
- ✓ A recent study showed that 2/3 of CLL patients had potentially significant drug interaction at time of commencing Ibrutinib, and another 8% during the course of treatment
- ✓ Elderly patients are commonly at risk of polyfarmacy due to multimorbidity

Yun S, et al; Clinical Lymphoma, Myeloma & Leukemia, 2017

IRAF: what we know

✓ In daily clinical practice, IRAF rates may be higher than in clinical trial setting

✓ Use of Warfarin or vitamin K antagonists was a controindication for enrollment in clinical trails

✓ CLL/MCL patients tend to have higher stroke risk due to advanced age and cardiotoxicity due to prior chemotherapies

✓ IRAF may require different risk assessment and anticoagulation approaches

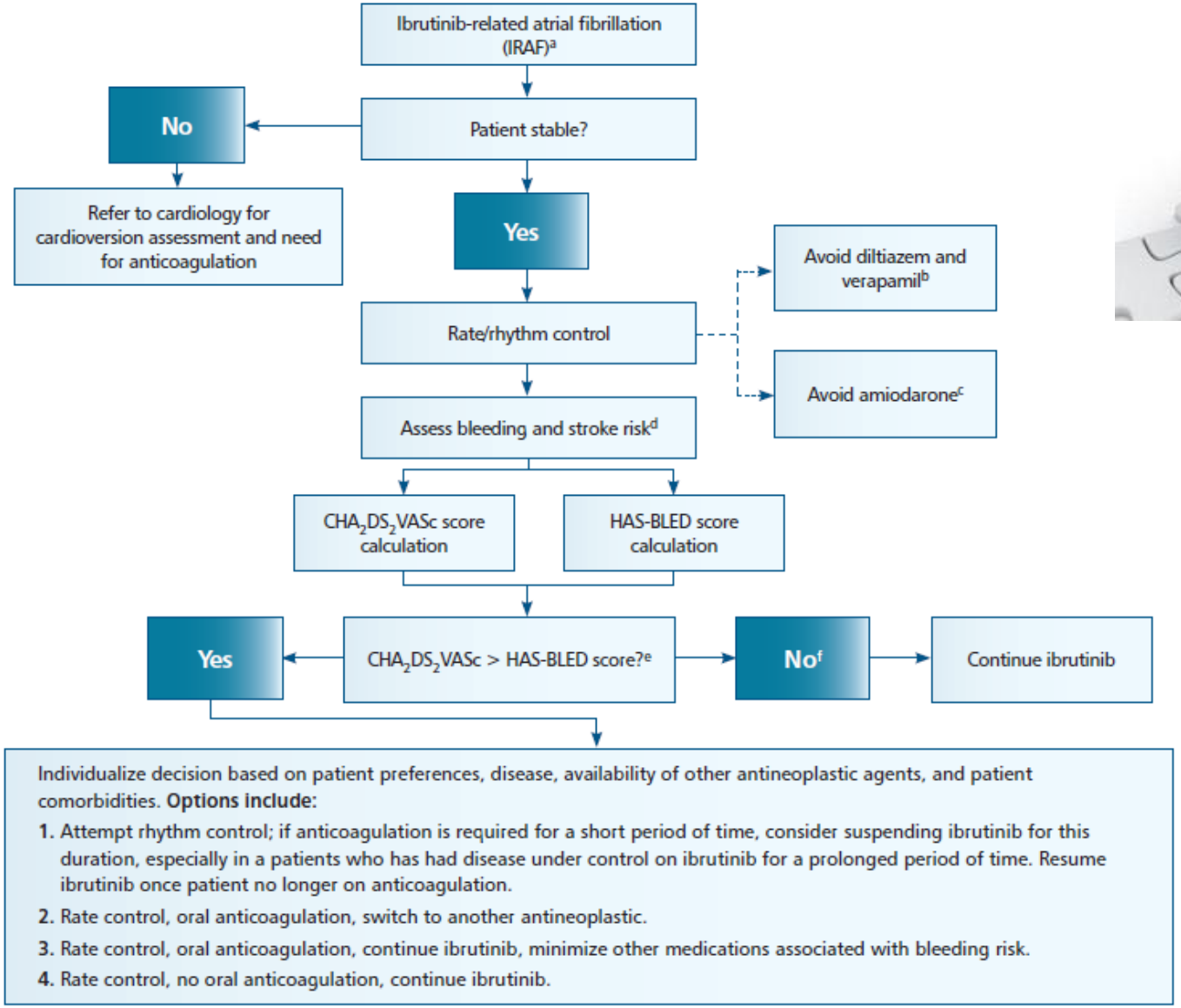
✓The clinical benefit of anticoagulation in AF/AFL in well established

✓ DOAC such as Dabigatran, Rivaroxaban and Apixaban were shown to have s

Outcome after Ibrutinib cessation for toxicity is poor. Thus, it is desiderable to continue therapy, whenever possible: a high rate of disease progression was seen in patients who stopped Ibrutinib, but not in patients who continue Ibritinib at reduced dose

Mulligan SP, et al; BJH, 2016
Hun JL, et al; Leukemia & Lymphoma, 2016

Algorithm for IRAF



Vrontikis A, et al; Oncology, 2016

Conclusion

Oncologists
treating patients with the best cancer therapies without adversely impacting cardiovascular health

Cancer therapy
may be abandoned because of an increased cardiovascular risk

Cardio-oncologists
developed in response to the combined decision making

Patients
receiving active and successful treatment are long-term survivors

GRAZIE PER L'ATTENZIONE!!!