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Patrocini richiesti

ARCA - INTERNATIONAL CARDIONCOLOGY SOCIETY - SIBioC - SIC

CARDIOTOSSICITÀ DA FARMACI ANTIEMETICI

Dott. Fausto Petrelli

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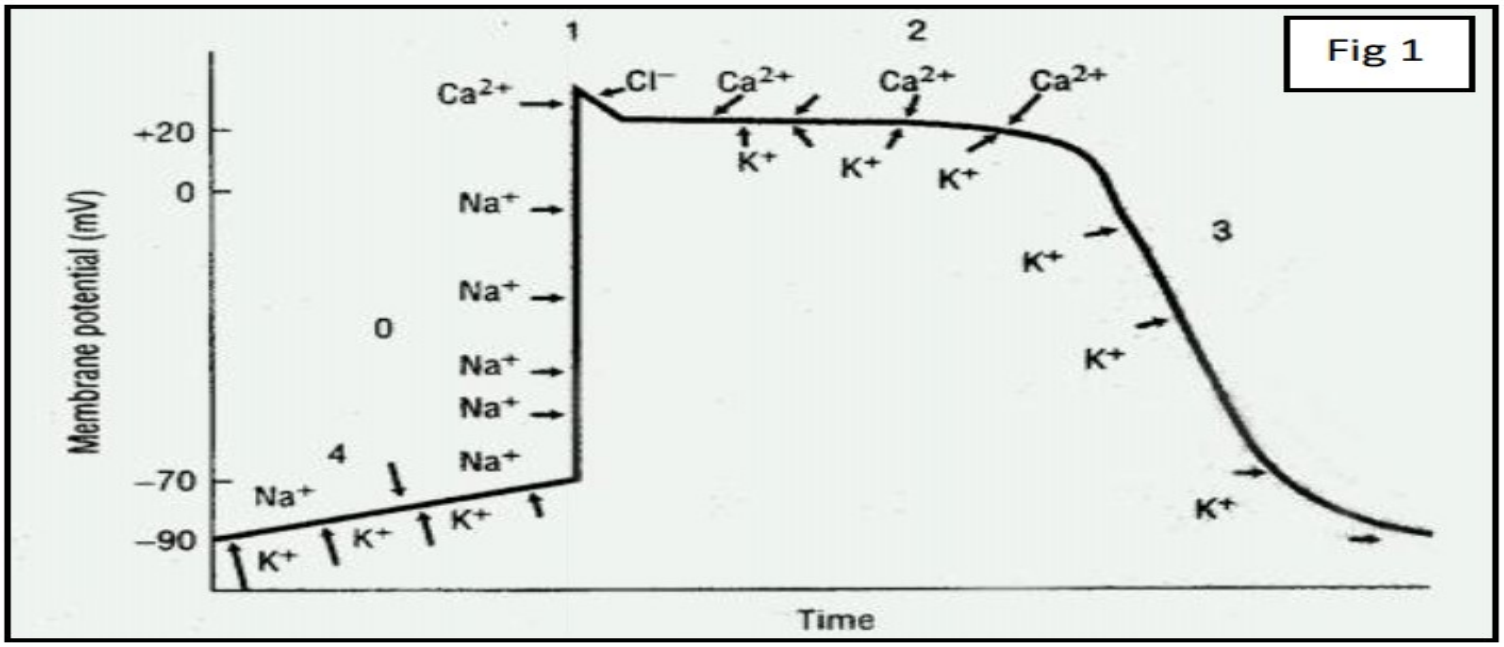
What's new in cardio-oncology regarding antiemetics?

- **Several drugs, oncologic and not, influence QT interval** that is the time between the start of the QRS complex and the end of the T wave in the ECG
- **In particular TKIs and anti-5-HT3 have the major effect on QT prolongation (risk factor for TdP)**
- These interaction has to be taken in mind when treating pts with cardiac morbidity, elderly or taking polypharmacy
- These events seems to be rare, idiosyncratic and asymptomatic but are reported in drug package insert
- Few years ago, AIFA lead to an alert for ondansetron risk of QT prolongation
- These drug are commonly used as antiemetics for MEC or HEC in clinical practice

Mechanism of cardiotoxicity

Granisetron, Ondansetron e Dolasetron block Na+ channels in a dose dependent manner and this can cause problems in repolarization, QT and QRS intervals



Tratto da: M. Leonard and M. Militello - 5-HT$_3$ Receptor Antagonists and ECG Effects Pharmacotherapy Update 20

Updated list of drugs associated with known/possibile risk of TdP used in oncology

- **Ondansetron**
- **Domperidone**
- ~~Dolasetron~~
- **Granisetron**
- **Tropisetron**
- *Metoclopramide (only under certain conditions)*

NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE E CON L'AGENZIA ITALIANA DEL FARMACO (AIFA)

1 Agosto 2014

DOMPERIDONE: nuove raccomandazioni per la minimizzazione dei rischi cardiaci.

Gentile Dottoressa, Egregio Dottore,

La presente nota La informerà sulle recenti raccomandazioni volte alla minimizzazione dei rischi cardiaci associati a domperidone, a seguito di una recente revisione dei benefici e dei rischi del prodotto.
Questa lettera è stata inviata in accordo con l'Agenzia Europea dei Medicinali (EMA) e con l'Agenzia Italiana del Farmaco (AIFA).

Riassunto:

- Il rapporto beneficio/rischio di domperidone rimane favorevole nel sollievo dai sintomi quali nausea e vomito negli adulti e nei bambini.
- Questa revisione conferma che esiste un lieve aumento del rischio di eventi avversi cardiaci gravi correlati all'uso di domperidone. È stato osservato un rischio più alto nei pazienti di età superiore a 60 anni, nei pazienti che assumono dosi giornaliere superiori a 30mg e nei pazienti che assumono in concomitanza farmaci che prolungano l'intervallo QT o inibitori del CYP3A4.
- Domperidone deve essere usato alla minima dose efficace per il minor tempo possibile. La durata massima del trattamento solitamente non deve eccedere una settimana.

- **Vandetanib**
- **Eribulin**
- **Crizotinib**
- **Dabrafenib**
- **Degarelix**
- **Lapatinib**
- **Leuprorelin**
- **Pazopanib**
- **Sorafenib**
- **Sunitinib**
- **Tamoxifen**
- **Vemurafenib**

www.crediblemeds.org (last revision: May 2

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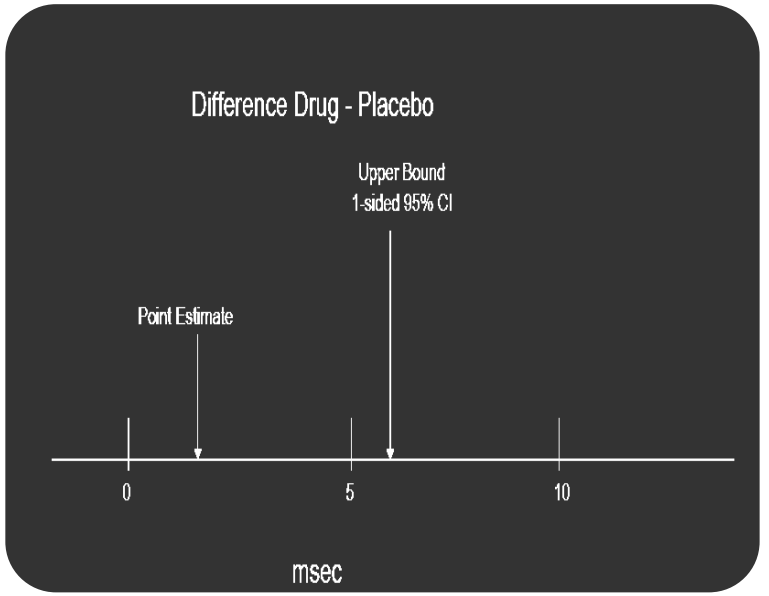
QT/QTc evaluation in clinical studies

Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

QTc prolongation is a surrogate marker of toxicity, used primarily for regulatory purposes, since the observations of TdP are a relatively rare phenomenon, hardly detectable in clinical pre-registration studies.



- ✓ **The assumption is that a small QT prolongation in a TQT could predict larger prolongations in patients.**
- ✓ **A positive study is defined as a drug-induced QT interval prolongation of approximately 5 milliseconds (ms), the threshold of regulatory concern, and is defined as a single-sided upper 95% confidence interval of less than 10 ms.**
- ✓ **Drugs that cause such a prolongation will be required to do extensive ECG collection and analyses in later stage studies.**

Nota informativa AIFA Agosto 2012

"Una dose singola per uso endovenoso di 16 mg diluita in 50-100 ml di soluzione iniettabile di cloruro di sodio 9 mg/ml (0,9 %) o altro fluido compatibile per infusione (vedere paragrafo 6.6) e somministrata per infusione, per almeno 15 minuti, immediatamente prima del trattamento chemioterapico.

Una singola dose per via endovenosa maggiore di 16 mg non deve essere somministrata a causa dell'aumento del rischio dose-dipendente di prolungamento dell'intervallo QT (vedere paragrafi 4.4, 4.8 e 5.1)."

http://www.agenziafarmaco.gov.it/sites/default/files/all_2_zofran_usr_dhcpl_final_03_08_sit

Through QT study

The Journal of Clinical Pharmacology
54(11) 1221–1229

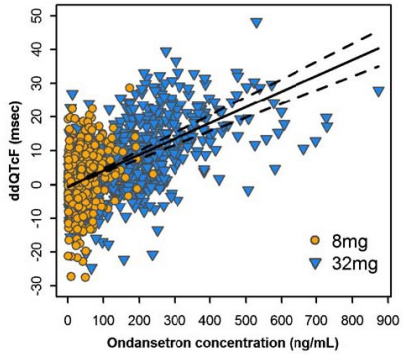
DOI: 10.1002/jcph.322

Integration of Modeling and Simulation to Support Changes to Ondansetron Dosing Following A Randomized, Double-Blind, Placebo-, and Active-Controlled Thorough QT Study

Treatment:

Treatment A: Single 8 mg IV dose of ondansetron infused over 15 minutes.
Treatment B: Single 32 mg IV dose of ondansetron infused over 15 minutes.
Treatment C: Placebo for ondansetron IV infused over 15 minutes.
Treatment D: Moxifloxacin provided as a single, oral 400 mg tablet.

Objectives: The primary objective was to characterize the effects of single intravenous doses of 8 mg and 32 mg ondansetron (given over 15 minutes) on QT duration corrected for heart rate by Fridericia's formula (QTcF) as compared to placebo.



Adults: IV single dose regimens		
8 mg over 15 min QD	90.4 (79.9, 102.4)	4.1 (2.3, 6.0)
16 mg over 15 min QD	194.9 (175.7, 216.3)	9.2 (7.3, 11.2)
24 mg over 15 min QD	292.4 (263.6, 324.4)	14.0 (12.0,16.3)
32 mg over 15 min QD	389.9 (351.5, 432.5)	18.9 (16.4, 21.3)
Elderly IV dose regimens		
8 mg (15 min) q4h x 3 doses (65–74 years)	133.7 (114.9, 155.6)	6.0 (3.0, 8.9)
8 mg (15 min) q4h x 3 doses (≥75 years)	166.6 (142.9, 194.1)	7.4 (3.6, 11.2)
16 mg & 8 mg (15 min) q4h x 2 doses (65–74 years)	183.6 (150.9, 223.5)	8.9 (5.8, 11.9)
16 mg & 8 mg (15 min) q4h x 2 doses (≥75 years)	232.8 (194.4, 278.8)	10.8 (6.8, 14.7)

Zuo, J Clin Pharmacol 2014

Post marketing data: ondansetron

Ondansetron and the Risk of Cardiac Arrhythmias: A Systematic Review and Postmarketing Analysis

Stephen B. Freedman, MDCM, MSc; Elizabeth Uleryk, BA, MLS; Maggie Rumantir, MD; Yaron Finkelstein, MD*

*Corresponding Author. E-mail: yaron.finkelstein@sickkids.ca.

Table 1. Summary of all secondary outcome reports identified from all sources searched.

	Pediatric (<18 Years) Reports			Adult (≥18 Years) Reports			
Source	**Intravenous**	**Oral**	**Intramuscular**	**Intravenous**	**Oral**	**Not Documented**	**Total**
Published literature	4	1*	1	12	1*	4	23
ADR databases							
VigiBase	4	0	0	19	0	2	25
FAERS†	1	0	0	8	0	3	12
Grey literature	0	0	0	0	0	0	0
Total	9	1	1	39	1	9	60

ADR, Adverse drug report; *FAERS*, FDA Adverse Event Reporting System.

*Involved long-term use (ie, multiple doses) in patients with significant arrhythmia risk factors.

†A total of 16 cases were identified in FAERS; however, 4 were duplicates of previously identified cases in VigiBase, yielding

49/60 segnalazioni in adulti

Freedman et al, Ann Intern Med, 2014

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Clinical data: ondansetron

Source	Pediatric (<18 Years) Reports (n=11)			Adult (≥18 Years) Reports (n=49)		
	Significant Medical History	Concomitant QT-Prolonging Medication	Prevention of PONV	Significant Medical History	Concomitant QT-Prolonging Medication	Prevention of PONV
Published literature	3	4	4	11	9	9
ADR databases						
VigiBase*	3	3	1	13	14	3
FAERS	0	1	1	10	9	3
Total (%)[†]	6 (55)	8 (73)	6 (55)	34 (69)	32 (65)	15 (31)

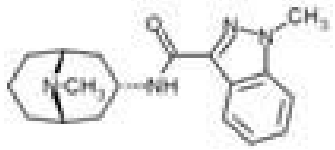
PONV, Postoperative nausea and vomiting.

*WHO global individual case safety report database system.

[†]Totals may underrepresent actual frequency of occurrence because all cases with missing or unclear information, particularly the ADR databases, had the item under consideration coded as negative (ie, not present).

Freedman et al, Ann Intern Med, 2014

Clinical data: granisetron



Granisetron

- **Granisetron also has a very high safety margin. However, it acquired a new safety warning in October 2009:**
  - ***An adequate QT assessment has not been conducted, but QT prolongation has been reported with granisetron. Therefore, granisetron should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders, as this might lead to clinical consequences.***

- In a industry-sponsored study, 240 subjects were randomized to 4 parallel treatment arms, including the two granisetron preparations (iv and TD), placebo, and oral moxifloxacin, 400 mg.

- **In the primary analysis, the maximum observed 90% upper confidence boundary was 6.88 msec, well below the threshold of 10 msec for regulatory concern.**

Mason et al, Cancer Mang Res,2014; Mason et al, Clin Cancer Res 2012

Alternative choices in high risk pts: granisetron patch

SICUREZZA CARDIOVASCOLARE

Assenza di effetti clinicamente e statisticamente significativi sul QTcF* o altre variabili elettrocardiografiche[1]

Table 3. Subjects with specific QTcF values and specific changes from baseline in mean QTcF (dQTcF) for each treatment group

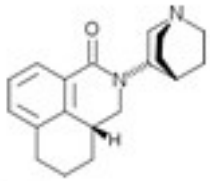
	Number of patients (%)			
Measurement	GTDS group 1 (N = 60)	Intravenous granisetron group 2 (N = 60)	Placebo group 3 (N = 60)	Moxifloxacin group 4 (N = 60)
QTcF				
>450, ≤480 ms	1 (2)	3 (5)	6 (10)	3 (5)
>480, ≤500 ms	0 (0)	0 (0)	1 (2)	0 (0)
>500 ms	0 (0)	0 (0)	0 (0)	0 (0)
dQTcF change				
>30, ≤60 ms	1 (2)	3 (5)	2 (3)	1 (2)
>60 ms	0 (0)	0 (0)	0 (0)	0 (0)

Tab.3 Rif. 1

*QTcF: Fridericia-corrected QT interval

Mason et al, Clin Cancer Res 2012

Alternative choices: palonosetron



Original Article
Supportive Care in Cancer
July 2012, Volume 20, Issue 7, pp 1507-1514

First online: 02 August 2011

A phase III open-label study to assess safety and efficacy of palonosetron for preventing chemotherapy-induced nausea and vomiting (CINV) in repeated cycles of emetogenic chemotherapy

Kenjiro Aogi ✉ , Hiroshi Sakai, Hirohisa Yoshizawa, Norikazu Masuda, Nobuyuki Katakami, Yasuhiro Yanagita, Kenichi Inoue, Masaru Kuranami, Mitsuhiro Mizutani and 1 more

✓ **A Phase III study of 358 cancer patients receiving chemotherapy**

✓ **Non QT interval alterations observed even in postmarketing phase!**

Table 3. Number and RR of potential risks

Class-related events	Total number of Adverse Reactions*	RR per 10^3 patients treated
Hypersensitivity reactions	46	0.0065
Constipation	27	0.0038
Convulsive events	8	0.0011
QT/QTc prolongation	0	0
Serotonin syndrome	0	0

* Total number of serious & non-serious events related to any ICSRs

Aogi K et al Support Care Cancer. 2012;20(7):1507-14.
Bertazzoli et al, ISoP 2014

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High dose palonosetron does not alter ECG parameters including QTc interval in healthy subjects: results of a dose-response, double-blind, randomised, parallel E14 study of palonosetron vs. moxifloxacin or placebo

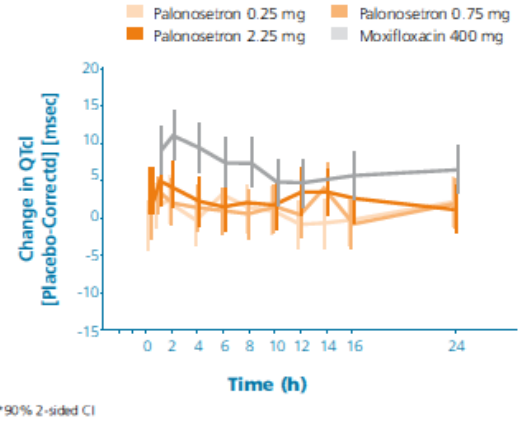
J. Morganroth[1], S. Parisi[2], T. Spinelli[2], C. Moresino[3], M. Thorn[4], M.T. Cullen[5]

[1]Clinical Professor of Medicine University of Pennsylvania School of Medicine and Chief Scientist, eResearch Technology Inc, Philadelphia PA, USA
[2]Helsinn Healthcare SA, Research and Development, Lugano, Switzerland [3]Helsinn Healthcare SA, Statistic and Data Management, Lugano, Switzerland
[4]Statistical Resources, Strategic statistical consulting, Chapel Hill NC, USA [5]MGI PHARMA, INC., Research and Development, Bloomington MN, USA

MATERIALS AND METHODS

- Potential effects on the individually corrected QTc interval (QTcI) were evaluated in a dose-response, placebo-controlled, double blind, randomised, parallel study on 230 volunteers (Table 1).
- Healthy subjects (18-65 years) were randomly assigned to one of five groups planned to contain 46 individuals:
  - Placebo IV + placebo oral
  - IV palonosetron at 0.25 mg + placebo oral
  - IV palonosetron at 0.75 mg + placebo oral
  - IV palonosetron at 2.25 mg + placebo oral
  - Oral (PO) moxifloxacin 400 mg + placebo IV (Positive control)

Figure 1. **Mean Changes in the Placebo-Corrected QTd Versus Time***



*90% 2-sided CI

Morganroth et al, Ecco 2007, poster presentation

Alternative choices: tropisetron

- ✓ **No published data on its effect on QT prolongation, up to date is not known its acute effects on cardiac repolarization**
- ✓ **In a prospective study conducted in 55 patients receiving chemotherapy it seems only slightly slow down the heart rate**

Yavas O et al. Support Care Cancer. 2008;16(9):1011-5

Studies including ECG monitoring

Table 1 Study characteristics

Reference	Study period, country	Study design, # of patients	5-HT3 dose/day	Intervention, examination timing	Outcomes examined
Hesketh [18]	NR, USA	Non-RCT, 44	IV dolasetron 1.2 mg/kg, 1.8 mg/kg, 2.4 mg/kg 30 mins before chemotherapy	ECG, 1–2 hrs and 24–48 hrs	PR, QT
Gralla [19]	August 2000 to October 2001, Germany, Italy, UK, Netherlands, Russia	RCT, 98	IV palonosetron 0.25 mg, IV palonosetron 0.75 mg, IV ondansetron 32 mg 30 mins before chemotherapy	ECG, 15 mins, 24 hrs, 1 wk	Mortality, QT
Kim [20]	April 2002 to October 2002, South Korea	RCT, 114	IV dolasetron 100 mg 30 mins before and 200 mg p.o. 2-5 days after chemotherapy, IV ondansetron 8 mg 30 mins before and IV ondansetron 16 mg 2–4 hrs plus an additional 16 mg/day p.o. 2-5 days after chemotherapy	ECG, 15 mins, 24 hrs, 1 wk	ECG findings unspecified

ECG: electrocardiogram; IV: intravenous; NR: not reported; Non-RCT: non-randomized clinical trial; p.o.: administered orally; RCT: randomized controlled trial.

No differences in ECG evaluations were observed between dolasetron or palonosetron versus ondansetron after 15 minutes, 24 hours, and 1 week post-administration in the 2 RCTs.

Minor increases in PR and QT intervals were observed in the NRCT for dolasetron dosages greater than 1.2 mg/kg 1–2 hours post-administration, but were deemed not clinically relevant.

Tricco et al, BMC Pharmacology and Toxicology 20

Spinelli *et al. SpringerPlus* 2014, **3**:389
http://www.springerplus.com/content/3/1/389

SpringerPlus
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RESEARCH Open Access

Effects of combined netupitant and palonosetron (NEPA), a cancer supportive care antiemetic, on the ECG of healthy subjects: an ICH E14 thorough QT trial

Tulla Spinelli[1]*, Cecilia Moresino[1], Sybille Baumann[2], Wolfgang Timmer[2] and Armin Schultz[2]

Table 2 Time-averaged analysis: mean changes from baseline

Endpoint	Parameter	Placebo (N = 50)	$NEPA_{200/0.5}$ (N = 48)		$NEPA_{600/1.5}$ (N = 49)		Moxifloxacin (N = 49)	
		Change from baseline	Change from baseline	Placebo-corrected change from baseline	Change from baseline	Placebo-corrected change from baseline	Change from baseline	Placebo-corrected change from baseline
Primary	QTd, ms	−2.1	2.6	4.7	1.5	3.6	6.3	8.4
	(Min;max)	(−8.3; 4.8)	(−5.8; 30.6)		(−7.3; 14.3)		(−2.6; 15.3)	

In conclusion, in this thorough QT trial, different NEPA combinations showed no ECG effects, which should predict a lack of cardiac safety concerns in clinical practice. Treatments were well tolerated.

NEPA/Dex vs PALO/Dex vs APREPITANT/5HT3/Dex

QTcF data	NEPA + DEX (all doses) (n = 1,442)	i.v./oral PALO + DEX (n = 1,600)	APR + OND/PALO + DEX (n = 238)
Baseline reference value (ms)	409.2 ± 19.86	410.5 ± 20.26	409.1 ± 20.71
5 hr postdose (ms)	420.8 ± 21.53	421.5 ± 21.07	418.0 ± 22.54
Change from baseline (ms)	11.5 ± 16.78	11.0 ± 16.76	9.2 ± 16.63
New values >500 ms	1 (0.1)	0	0
Increase by >60 ms	2 (0.1)	4 (0.3)	2 (0.8)
24 hr postdose (ms)	419.8 ± 22.74	419.0 ± 21.79	416.0 ± 21.31
Change from baseline (ms)	10.6 ± 18.85	8.6 ± 18.52	7.2 ± 16.05
New values >500 ms	2 (0.1)	1 (0.1)	0
Increase by >60 ms	5 (0.3)	9 (0.6)	1 (0.4)
120 hr postdose (ms)	407.3 ± 20.56	410.4 ± 21.08	406.5 ± 20.41
Change from baseline (ms)	−1.9 ± 17.15	−0.2 ± 18.68	−2.3 ± 16.92
New values >500 ms	0	0	0
Increase by >60 ms	3 (0.2)	2 (0.1)	1 (0.4)

Unless otherwise noted, values are n (%).
Abbreviations: AE, adverse event; APR, aprepitant; DEX, dexamethasone; ms, milliseconds; NEPA, netupitant + palonosetron combination therapy; OND, ondansetron; PALO, palonosetron; QTcF, QT interval corrected for heart rate according to Fridericia's formula.

In this analysis, cardiac AEs and changes in ECG measures were similar in all groups, with a low incidence of serious cardiac TEAEs, indicating an acceptable cardiac safety profile. Few patients experienced QTcF >500 milliseconds or increases > 60milliseconds from baseline across all 3 groups.

Aapro et al, Oncologist 2016

4 trial assessed a transdermal granisetron regimen versus a palonosetron regimen for patients receiving MEC; transdermal granisetron was not inferior to palonosetron in preventing nausea and vomiting in the acute stage.[105]

The addition of dexamethasone improves the efficacy of the antiemetic regimen containing 5-HT3 antagonists (see *Dexamethasone* in this Discussion). However, dexamethasone is associated with side effects (such as insomnia). When dexamethasone is used with palonosetron for MEC, a randomized trial suggests that the dose of dexamethasone can be decreased to 8 mg on day 1 and also eliminated on days 2 to 3.[106]

Cardiac Side Effects

Ondansetron, granisetron, and dolasetron have been associated with an increased risk for developing abnormal electrical activity of the heart (detectable on ECG, including prolongation of electrocardiographic intervals such as PR or QT intervals). However,[99,100,107-114] this warning is not in the package inserts for palonosetron, granisetron extended-release injection, and the granisetron transdermal patch. Although the ECG changes can be reversible and asymptomatic, abnormal activity can also result in potentially fatal cardiac arrhythmias (including torsade de pointes) in some cases. Patients who may be particularly at risk for developing torsade de pointes include those with congenital long QT syndrome or other underlying cardiac diseases, congestive heart failure, bradycardia, those with electrolyte abnormalities (eg, hypokalemia, hypomagnesemia), and those taking other medications that can lead to QT prolongation. Routine ECG monitoring during treatment with[99] regimens that include 5-HT3 antagonists may be useful for these[100,111,115] patients who may have concomitant risk factors for QT prolongation. As previously mentioned, intravenous dolasetron is no longer recommended for the prevention of nausea and vomiting because it has been associated with an increased risk for cardiac arrhythmias.[99,100]

Palonosetron

Palonosetron is a 5-HT3 antagonist with an approximately 100-fold higher binding affinity for the 5-HT3 receptor compared to ondansetron, granisetron, and dolasetron. Palonosetron has a half-life of approximately 40 hours, which is significantly longer than other commercially available 5-HT3 antagonists.[53] Data suggest that palonosetron is associated with prolonged inhibition of the 5-HT3 receptor and thus differs from ondansetron, granisetron, and dolasetron.[116,117] By suppressing cross talk between 5-HT3 and NK1 signaling pathways, palonosetron may indirectly inhibit substance P.

Several randomized phase 3 trials have assessed the efficacy of palonosetron compared with other 5-HT3 antagonists in preventing emesis associated with both moderate and high emetic risk chemotherapy regimens, particularly for delayed emesis.[70-75] In these studies, the primary efficacy endpoint was CR, defined as having no emesis and no rescue treatments. In a study in patients receiving MEC (N = 563 evaluable), a single dose of palonosetron (0.25 mg intravenous) was found to be superior to a single dose of ondansetron (32 mg intravenous) in preventing both acute (CR rate, 81% vs. 69%; $P < .01$) and delayed emesis (CR rate, 74% vs. 55%; $P < .01$); no concomitant corticosteroids were given in this study.[73] The safety and side-effect profiles of palonosetron were indistinguishable from the control 5-HT3 antagonists (ondansetron and dolasetron). Note that the FDA now recommends a maximum of 16 mg for a single dose of intravenous ondansetron.[99]

In a phase 3 randomized trial that compared palonosetron with ondansetron in patients receiving HEC (N = 667), the majority (67%)

What's suggesting to our cardiologist?

- **Strict monitoring of high risk pts using drugs potentially leading to QT prolongation (baseline ECG!)**
- **Provide cardiologist all past ECGs and list of drugs used**
- **Inform immediately any change of drug assumed**
- **Periodic update of QT-interval influencing drug's list**
- **Strict collaboration even with patient's general physician**

Conclusions and take home messages

- We have to be aware that some antiemetics used in clinical practice are associated with a small risk of QT prolongation
- High risk patients need to be indentified and treated differently (e.g no or reduced dose (≤16 mg)/rate of infusion (≥15') ondansetron)
- Strict ECG monitoring seems not useful for all pts (utility up to 5' after infusion!)
- Put attention to association with other drugs potentially associated with toirsade de point
- It is preferable to change antiemetic if risk is perceived as relevant (e.g *palonosetron or granisetron TD*)
- Monitoring in particular those with congenital QT syndrome, women, cardiovascular patients, those with polypharmacy/electrolytes imbalance, elderly is advisable.