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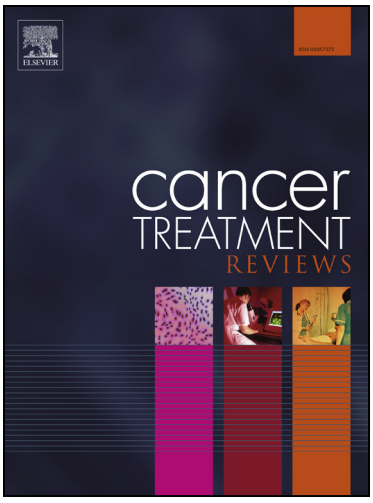

Management of QT prolongation induced by anti-cancer drugs: target therapy and old agents. Different algorithms for different drugs.

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Management of QT prolongation induced by anti-cancer drugs: target therapy and old agents. Different algorithms for different drugs.

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Prolongation of the corrected QT (QTc) and cardiac arrhythmias

QT interval recorded by electrocardiogram (ECG) reflects the overall duration of ventricular activation and recovery [2]. QT prolongation is almost always subsequent to cardiac repolarization abnormalities. Many drugs, making dysfunctional subunits of voltage-gated channels can cause a wide spectrum of events, from QT prolongation, to ventricular tachycardia, until his sudden death.
Various correction formulas have been developed to improve QT measurement accuracy (fig.1), among these the most widely used in clinical practice are the Balzett and the Fredericia formulas [2-7]. In fact, in case of altered cardiac frequencies, heart rates higher than 100 beats per minute (bpm) or lower than 60 bpm, the correction according to Bazett is not ideal because the value is overestimated or underestimated, respectively, and the use of the Fridericia's formula is preferred.
QT prolongation can be associated to a ventricular tachycardia, known as torsades de pointes (TdP), that can degenerate into a ventricular fibrillation, usually with a fatal outcome. Torsades de Pointes is characterized by QRS complexes that oscillate around the isoelectric and vary in morphology and continuous voltage.
The NCI classification of the 4 degrees of QT prolongation associated with anticancer drugs is as follows: grade 1, QTc 450-480 ms; grade 2, QTc 481-500 ms; grade 3 QTc > 501 ms on at least two separate electrocardiograms; grade 4 QTc > 501 ms or a change of > 60 ms from baseline and TdP, polymorphic ventricular tachycardia, or signs or symptoms of severe arrhythmia [8].
It is difficult to assess the risk of developing life-threatening arrhythmias from QTc prolongation syndrome [9-10], although there is a clear correlation among prolonged QTc interval, incidence of TdP and sudden death. In each case, the total risk of potential fatal ventricular tachycardia is low [9].
Several factors can cause QT prolongation in patients with cancer [11,12]:
1. Anti-cancer drugs: arsenic trioxide (ATO), ceritinib, crizotinib, dasatinib, nilotinib, lapatinib, panobinostat, pazopanib, romidepsin, sorafenib, sunitinib, vandetanib, vemurafenib, vorinostat; the algorithms of QT prolongation induced by some of these drugs have been reported by Yeh on Onco-Cardiology [12];
2. Co-existing risk factors (among the non-cardiac: hypothyroidism; among the cardiac: congenital long QT syndrome, left ventricular dysfunction, myocardial ischemia);
3. Concomitant treatments: antidepressants, antiemetics, antibiotics, antipsychotics, anti-fungal syndrome, anti-histamines and methadone;
4. Side effects associated with cancer therapy: nausea and vomiting, dehydration followed by electrolyte imbalances like hypokalaemia, hypomagnesaemia, hypocalcaemia; other effects are kidney failure, liver dysfunction and poorly controlled diabetes.
Therefore, it is mandatory that patient care is improved by knowledge of the different classes of anti-cancer drugs associated with QTc prolongation (arsenic trioxide-ATO, anthracyclines, angiogenesis inhibitors, epidermal growth factor receptor 2-HER2/ErbB2 inhibitors, Abelson murine leukaemia viral oncogene homolog 1-ABL inhibitors, histone deacetylase–HDAC inhibitors and other various agents), a careful data collection using the "tangent" method for the measurement of the QT interval and the Balzett and Fredericia formulas for heart rate correction (fig.2); the identification of risk factors and correction of electrolyte abnormalities, particularly for potassium

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and magnesium as well as careful evaluation of concomitant drug treatment, cardiac or not, that prolong the QT interval (eg, antiarrhythmic agents, diuretics, anti-anginal, antifungals, antibiotics, antiemetics, psychotropic drugs, etc.) [11-14]. In figure 3 is shown the algorithm for the management of the QT prolongation during antineoplastic therapy in use in our centre [14].

Angiogenic inhibitors

Angiogenesis inhibitors work by blocking vascular endothelial growth factor (VEGF) and its receptors. For their lower binding specificity, tyrosine kinase inhibitors (TKIs), are multi-target agents and consequently they exhibit pronounced cardiotoxic effects [15,16].
Among these drugs, vandetanib and sunitinib are the ones that more often have been associated with QT prolongation, while the risk associated with other vascular endothelial growth factor receptors (VEGFRs) TKIs, including sorafenib, is less certain [16]. In a meta-analysis that included 18 randomized controlled trials with a total of 6548 patients, it was assessed the risk of QTc prolongation associated with VEGFR TKIs (sunitinib, axitinib, vandetanib, cabozantinib, sorafenib, pazopanib, ponatinib and regorafenib) [17]. Overall, 4.4% of patients had some QTc prolongation, of every NCI classification degree, while only in the 0,83% of exposed patients occurred a severe lengthening of the QTc interval. In the subgroup analyses, sunitinib and vandetanib were both associated with a statistically significant risk of QTc prolongation, while the increase of RR risk observed was not statistically significant [16]. Higher doses of vandetanib were associated with an increased risk (RR 10.60 against 4.83 for lower doses). The rate of serious arrhythmias, including TdP does not seem to be greater in patients who have developed a high degree of QTc prolongation. The risk of QTc prolongation was independent from the duration of therapy [17].
It is very important to check the possible inhibition of cytochrome P450 3A4 (CYP3A4) by concomitant medications that may increase plasma concentrations of many of the antiangiogenic TKIs and for which, for this reason, it may be required a dose reduction. There are evidences that the drug-induced QT prolongation is due to PI3K signalling inhibition, with effects on many ion channels and not only on those of potassium [18,19].

Vandetanib

In several clinical trials, vandetanib was associated with QTc prolongation, TdP and sudden death [16,20,21]. A meta-analysis including nine clinical studies, phase II or III, for a total of 2,188 cancer patients, showed that treatment with vandetanib is associated with a significant increase in overall incidence and risk of QTc prolongation. This is true for thyroid cancer and other cancers such as breast cancer and lung cancer [21]. Typically QT prolongation is dose-dependent and occurs frequently at the beginning of three months of treatment [22].
Because of its cardiovascular risk, vandetanib requires careful correction of hypocalcaemia, and / or hypomagnesaemia. Moreover, since drug half-life is very long (19 days), it is recommended to perform a basic ECG at 2, 4, 8 and 12 weeks after initiation of treatment and every three months. Monitoring of electrolytes and calcium, as well as thyroid stimulating hormone (TSH) is recommended [22]. Vandetanib is not advisable in patients with QTc > 480msec.

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Patients, in which QTc interval prolongation is greater than 500 ms during treatment, should stop the medication until the QTc interval returns to values less than 450 ms; you can then re-administering the drug at a reduced dose [22].

Pazopanib

Pazopanib is a powerful multi-targeted TKI that targets VEGFRs, platelet-derived growth factor receptors (PDGFRs) and c-Kit receptor [23]. Pazopanib is mainly approved for the treatment of advanced renal cell carcinoma and, in adult patients, for subtypes of sarcoma [24,25].
Pazopanib determines QT prolongation (> 500 ms) in 2% of cases. The incidence of TdP is <1% [26]. It must be used with caution in patients with heart disease or who are taking antiarrhythmics or other drugs known to prolong the QT.

Sunitinib and sorafenib

Sunitinib is a multi-targeted TKI that bind and inhibits VEGFRs 1-3, c-Kit, PDGFRs A and B, rearranged during transfection (RET) receptor, Fms-like tyrosine kinase 3 (FLT3) receptor and colony stimulating factor receptor (CSF1R), indicated for the first-line treatment in renal cell carcinoma and second-line in patients with GastroIntestinal Stromal Tumors GIST [27].
Sorafenib is another multitarget TKI against VEGFRs 2-3, PDGFRs b, c-Kit, FLT3, and BRAF RAF1 indicated for the second-line treatment against renal cancer and hepatocellular carcinoma [28].
Although the use of these medications has revolutionized the treatment of certain malignancies, during the last years we have gathered enough evidence on their potentially fatal adverse cardiovascular effects [29-32].
While sunitinib has a dose-dependent effect on QTc interval, the effect of sorafenib on the performance of QTc appears modest and is unlikely to be of clinical relevance [2,16,33,34,35]. However, since the prolongation can cause an increased risk of ventricular arrhythmias, although minimal, sunitinib must be used with caution in patients treated with drugs known to prolong the QT, as well as in patients with bradycardia, or electrolyte abnormalities [36].
In general, in patients treated with sunitinib we perform ECG at baseline and during treatment only if patients are also receiving other potential QTc prolonging drugs [33,34].

ErbB2 inhibitors

Lapatinib

Lapatinib is a TKI used in the treatment of HER2-positive metastatic breast cancer [37].
Lapatinib is the only ErbB2 inhibitor associated with QTc prolongation. In one study, uncontrolled, open-label, in patients with advanced cancer there was an increasing of the QTc interval dependent on the concentration of the drug [37].
Lapatinib must be administered with caution under conditions that may favour QT prolongation, as electrolyte disorders (hypokalaemia, hypomagnesaemia), congenital long QT syndrome and concomitant administration of QT prolonging drugs [36]. In any case, before and during the administration of lapatinib, we recommend to correct any hypokalaemia and hypomagnesaemia and to perform ECG with QT measurement (fig.4) [37].

ABL inhibitors

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Dasatinib and Nilotinib

The BCR-ABL inhibitors currently approved by the Food and Drug Administration (FDA) for the treatment of chronic myeloid leukaemia (CML) are imatinib, dasatinib and nilotinib. CML is a blood disorder that rushes in 15-20% of adults with leukaemia. This disorder is characterized by the presence of the Philadelphia chromosome (Ph + CML) that arises from a reciprocal translocation between chromosome 9 and 22 [38]. Nilotinib and dasatinib are BCR / ABL1 second-generation multitarget TKI, both associated with QT prolongation [2]. Recommendations on the use of nilotinib and dasatinib are the following [39-40]:

- If QTc > 480 msec and serum electrolytes are not within normal limits, we must correct the electrolyte abnormalities that may be present and verify the possible use of QT prolonging drugs;
- If QTc > 480 msec and serum electrolytes are within normal limits you can begin treatment by repeating the ECG and re-evaluating serum electrolytes after 7 days.

After this time:

If QTc > 480 msec it is recommended to discontinue treatment, correct the disionia and check for the concomitant use of QT prolonging drugs;

- If QTc (QT) returns < 450 msec, resume the drug at the previous dosage;
- If QTc returns to 450-480 msec, reduce the dose to 400 mg once daily;
- If QTc interval > 480 msec even after the reduction of the dosage to 400 mg once a day, treatment must be interrupted.

Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDACi) are a family of nuclear proteins that interact with the DNA by blocking the activity of histone deacetylase, involved in the activation and deactivation of genes, through the removal of acetyl groups that stabilizes the interaction between DNA and histones.

HDACi, an emergency class of drugs with potential anti-neoplastic activity, have multiple effects *in vivo* and *in vitro* specific for each cell type, like: growth arrest, cell differentiation interference and induction of apoptosis of malignant cells.

Both vorinostat and romidepsin, two HDACi approved in the US for the treatment of cutaneous T-cell lymphoma, can cause ECG changes and QTc prolongation [41-43]. This occurs in some, but not all, of the reviewed studies. Vorinostat that turn-off genes involved in the cellular division, is also designed for other types of cancers including advanced lung cancer and no small cell lung cancer (NSCLC).

Routine ECG monitoring is recommended for both drugs, although they must be used with caution in patients with pre-existing cardiovascular disease, congenital long QT syndrome, and in those receiving concomitant QTc prolonging drugs or that inhibit the cytochrome P450 (CYP450), which is the main enzyme responsible for the metabolism of vorinostat and romidepsin [44,45]. Even in this particular case, we recommend attention to potassium and magnesium levels [44,45].

Another HDACi, panobinostat, used in the treatment of refractory multiple myeloma, is known to have a potential cardiotoxic effect, including QTc prolongation [46]. The same considerations on electrolytes and concomitant drugs are valid also for panobinostat. Moreover, it is contraindicated in patients with a recent history of myocardial infarction or unstable angina, and in patients with a QTc interval> 480 msec or significant abnormalities of ST or T-wave [45, 47]. In figure 5 is reported the algorithm for the management of QTc prolongation induced by panobinostat.

Various agents

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Arsenic trioxide

Arsenic trioxide (ATO) is an effective agent for the treatment of patients with acute promyelocytic leukaemia (APL) who are relapsed or refractory to trans retinoic acid and chemotherapy with anthracyclines. Recent data have demonstrated its efficacy, as single agent, in primary therapy (APL) [48-50]. However, ATO can cause QT prolongation and lead to potentially fatal ventricular arrhythmia, as TDP [51-54].

The risk of TdP is related to various conditions: co-administration of drugs known to prolong QT, TdP history, pre-existing QT interval prolongation, or other conditions that lead to hypokalaemia or hypomagnesaemia [55,56].

In a retrospective analysis conducted to determine the degree of QT prolongation in 99 patients with advanced cancer treated with ATO, 35.4% of patients experienced QT prolongation > 60msec [55-57], one patient, affected by hypokalaemia, developed asymptomatic TdP, which resolved spontaneously and is not relapsed after electrolyte correction. No case of sudden death and/or arrhythmia-related deaths was found. In conclusion, this analysis shows that ATO can prolong the QTc interval. However, by a proper ECG monitoring and electrolytes check, it can be safely administered in patients with APL.

Vemurafenib

Vemurafenib, an oral inhibitor of the mutant BRAF protein (V-raf murine sarcoma viral oncogene homolog B1), is approved for the treatment of metastatic melanoma with BRAF V600E mutation [58]. Vemurafenib is associated with QTc prolongation, so ECG and electrolytes monitoring are recommended before treatment and after any dose modification. For patients treated with vemurafenib, ECG should be carried out at baseline, after 15 days of treatment, every month during the first three months of treatment and every three months, more often if clinically indicated. If the QTc interval exceeds 500 msec, treatment should be temporarily interrupted with correction of any electrolyte abnormalities [36]. Therefore, a dose of 720 mg can be taken twice a day (or 480 mg twice daily if the dose has already been lowered). In case of a third manifestation of QT> 500msec, treatment suspension is recommended.

Crizotinib and ceritinib

Crizotinib and ceritinib are oral inhibitors of anaplastic lymphoma kinase (ALK), and they have been approved for the treatment of advanced cancer or metastatic NSCLC [59,60]. Only in some cases, it has been observed QTc prolongation, and therefore this anomaly is not frequent. Only in the 3% of 255 patients treated with ceritinib it was observed an increase of the QTc interval by 60 msec from baseline. While in another study conducted on 304 patients treated with the same drug, there was a lengthening of QTc interval > 500 msec in only one patient (<1 percent) [61,62]. Treatment suspension and dose reduction are indicated if QTc prolongation is greater than 500 msec, while discontinuation is mandatory in case of recurrence or arrhythmia, HF, hypotension, shock, syncope or TdP [62,63].

Even crizotinib is associated with QTc prolongation with a feasible risk of ventricular tachyarrhythmia event. For this reason, before starting the treatment is necessary to consider benefits and potential risks, paying particular attention to patients with pre-existing bradycardia, taking anti-arrhythmic medicines or other drugs known to prolong QT interval and in patients with significant heart disease pre- existing and/or electrolyte disturbances [62,63]. In figure 6 is shows the algorithm for the management of crizotinib.

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Immunotherapy

QT prolongation can be induced by the block of rapidly activating delayed rectifier potassium channel, encoded by the human ether-a-go-go-related gene (*hERG)* [64,65]. Usually drugs associated with Qtc prolongation are small molecules, but also biologic anticancer agents, with high molecular weights (> 140 kDa), seem to have an interaction with hERG. Among these, the most promising is nivolumab, a fully human IgG4 (S228P) monoclonal antibody that binds and blocks the programmed cell death 1 (PD-1) receptor [65]. It is used in the treatment of melanoma, NSCLC, renal cell carcinoma (RCC), relapsed or refractory Hodgkin lymphoma and in a growing list of other tumours [65].

A recent study on patients receiving nivolumab showed that this agent has no clinically meaningful effect on QTc interval when administered at doses up to 10.0mg / kg.

PARP Inhibitors

Polymers (ADP-ribose) polymerases 1 and 2 (PARP-1 and PARP-2) are very abundant enzymes in the cells, with nuclear localization. They have a catalytic activity NAD+ dependent that determines the synthesis of a negatively charged polymer called poly-ADP-ribose (PAR) and transfers it to the target proteins. Such enzymes are involved in many biochemical activities that control structural and regulatory functions and thus processes such as DNA transcription and repair, cycle regulation, and cell death. In particular, PARP-1 and PARP-2 are essential components of the Base Excision Repair (BER) which is involved in the repair of DNA-induced radiation and methylating agents damages. Inhibition of PARP activity causes cell death for apoptosis. In recent years, PARP inhibition highlighted to potentiate the cytotoxicity of Dna-damaging chemotherapy and ionizing radiation and represents a good strategy for the treatment of cancer with homologous recombination deficiency (eg. BRCA mutation) [66].

Rucaparib

Rucaparib was the first approved PARP inhibitor used in the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer that have been treated with two or more chemotherapies (Study 42, ClinicalTrials.gov NCT01078662) [67,68]. The safety of rucaparib was evaluated in 377 patients with advanced ovarian cancer [69]. The most common side effects reported by patients were nausea, fatigue/asthenia, vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. No clinically relevant effect on QTc prolongation has been observed, when rucaparib was administered at a dose of 600mg orally twice daily as monotherapy [69].

Niraparib

Niraparib is a PARP inhibitor indicated in the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that are in a complete or partial response to platinum-based chemotherapy [70].

Treatment with niraparib is not associated with any clinically relevant effect on QTc prolongation. In the NOVA study, grade 3-4 hypertension occurred in 9% of niraparib patients compared to 2% of placebo patients [71].

Veliparib

Veliparib (ABT-888) is an orally bioavailable potent PARP inhibitor. In the Phase I study conducted by Munasinghe et al, patients with advanced solid tumors treated with single doses of

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veliparib (200mg or 400mg) did not experienced any clinically relevant effect on QTcF prolongation [72].

CEP-9722

CEP-9722 is a pro-drug of CEP-8983, a potent PARP-1/-2 inhibitor. The Phase 1 dose-escalation study demonstrated that CEP-9722, used as monotherapy or in combination with temozolomide in patients with solid tumor, was well tolerated and no clinically significant abnormalities were showed [73]. Central review of ECGS showed no clinically significant abnormalities.

Olaparib

Olaparib is an FDA approved drug for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy. The antitumor efficacy of Olaparib has been demonstrated in fase II and III studies [74,75]. In the clinical trial conducted by Tutt *et al*, the efficacy, safety, and tolerability of olaparib were tested in women with *BRCA1* or *BRCA2* mutations and advanced breast cancer [76]. No significant changes in the ECG was observed during treatment with a lower dose (100 mg twice daily) of olaparib and a maximum tolerated dose (400 mg twice daily), compared to the baseline. In the Phase I study, Swaisland *et al*, confirmed that no clinically relevant effect of olaparib on QT interval was observed in 119 patients treated with a single dose of 300mg and in 109 patients following multiple dosing of 300mg BID [77].

CDK4/6 Inhibitors

CDKs 4/6 (Cyclin-dependent kinases) are members of the protein kinase family. Their kinase activity is regulated by proteins called cyclins. The active kinase complex, cyclin-CDK4/6, regulates the cell cycle during G1/S transition. Cyclin binding, CAK phosphorylation, regulatory inhibitory phosphorylation and binding of CDK inhibitory subunits (CKIs) represent the main mechanisms of this protein kinase family. G1-to-S regulatory machinery is impaired in main cancer cells, due to the deregulated expression of D-type cyclins, resulting in a hyperactivation of CDKs 4/6, or to an improper formation of cyclin D1 complexes with CDKs 4/6.

CDKs inhibitors are molecules that prevent the formation of an active kinase complex, thus inhibiting their activity.

Ribociclib

Ribociclib is a cyclin dependent kinase 4 and 6 (CDK4/6) inhibitor used for the treatment of postmenopausal women hormone receptor positive (HR+), human epidermal receptor 2 negative (HER2-) advanced breast cancer [78].

In the randomized, double-blind, placebo-controlled, Phase III study, MONALEESA-2, the events of QT prolongation experienced by patients were reversible and managed by dose interruptions and reductions, without any clinical consequences [79].

Recommendations for the management of treatment with ribociclib include ECG examination at baseline, on day 14 of cycle 1 and at the beginning of cycle 2, serum electrolytes (including potassium, magnesium, calcium, and phosphorous) monitoring prior to treatment and at the beginning of the first 6 cycles, as clinically indicated. Any electrolyte abnormalities must be

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corrected prior to treatment. Based on the severity of QT prolongation the treatment may require interruption, dose reduction and/or discontinuation [80].
Treatment with ribociclib is recommended only in patients with QTcF <450 msec. The use of this drug in patients at high risk for developing QTc prolongation, including patients with long QT syndrome, uncontrolled or significant cardiac disease (eg, recent MI, HF, unstable angina, bradyarrhythmias) must be avoid. Moreover, the concomitant use of ribociclib with any medications known to prolong the QTc interval and/or strong CYP3A inhibitors, which may prolong the QTcF interval, is severely discouraged.

Palbociclib

Palbociclib is a reversible, highly selective, CDK4/6 inhibitor developed by Pfizer. In 2015, it was approved by FDA in combination with letrozole, for the treatment of ER-positive advanced breast cancer [81,82]. The efficacy and safety of this drug was investigated in the PALOMA-1 (phase II) and PALOMA-2 (phase III) trials, where women with advanced or metastatic breast cancer, ER-positive and HER2-negative, were treated with palbocinib in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women, or fulvestrant in women with disease progression after endocrine therapy, respectively [83-86]. No evidence of QTc interval prolongation was observed either in the subgroup of 125 patients enrolled in the PALOMA-2, or in patients enrolled in the PALOMA-1 trial, at the recommended dosing regimen [87, 88].
The randomized phase 3 trial, PALOMA-3, evaluated the combination of fulvestrant plus palbociclib versus fulvestrant plus placebo in pre- and postmenopausal women with HR-positive/HER2-negative advanced breast cancer [89,90]. In the palbociclib plus fulvestrant arm, 1 patient experienced QT prolongation (SAE of grade 3), which resolved within 2 days [91].
In the phase 1/2 study on safety and efficacy of palbociclib with bortezomib and dexamethasone in relapsed/refractory multiple myeloma, none of the patients experienced QTc interval prolongation >500 msec and 3 patients had a maximum increase from baseline of ≥60 msec [92].
In another phase 1 study on solid tumors, none of the patients had a QTc value of >500 msec [93,94].

Abemaciclib

Abemaciclib is another CDK4/6 inhibitor, developed by Eli Lilly, used in the treatment of advanced or metastatic breast cancers [95].
The safety and efficacy of this drug, used as monotherapy in metastatic breast cancer, was evaluated in 132 women enrolled in the phase II study, Monarch 1 [96]. Only 1 patient discontinued the treatment due to QT prolongation.
The phase 3 study, Monarch 2, compared the efficacy and safety of abemaciclib at a dose of 150 mg twice daily, plus fulvestrant, at a dose of 500 mg, with fulvestrant alone in patients with advanced breast cancer [17]. No QT prolongation event was reported from the study [87,97].

Conclusions

Patients undergoing chemotherapy have a higher risk of developing cardiovascular complications, and the risk is even greater if there is a history of heart disease. Moreover, anthracyclines, together with a wide range of biological molecules, such as trastuzumab and ErbB2 inhibitors, are well known to have cardiotoxic effects.

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Each anticancer drug could potentially have "on target" or "off target" cardiotoxic effect.
Although the incidence of QT prolongation induced by drugs is generally low, it is one of the cardiovascular complications that oncologists and cardiologists have to deal with.
The effect of these molecules on QT prolongation is variable, for example in the treatment with ATO, QT prolongation was observed 1-5 weeks after infusion, and this spontaneously returned to baseline values after 8 weeks from the begging of the therapy [54]. In contrast, for the treatment with vandetanib is recommended to monitor ECG and QT interval at baseline, at 2-4 weeks and at 8-12 weeks after the start, and every three months [22].
Considering the high variability in the management, there are several ongoing clinical trials to evaluate how TKIs and other new drugs can affect the QT interval.
A work recently published by Diemberger *et al*. confirms the high prevalence of QTc prolongation after chemotherapy [64]. Patient follow-up scheme proposed by the authors enable to identify with high sensitivity, based on the initial QTc values, those who must continue ECG monitoring and those who, being at low risk, should not necessarily repeat the ECG. The study identifies in the age and in the initial/post first cycle QTc, two independent predictors of prolongation, during treatment, QTc> 470/480msec.
Moreover, Cuni *et al*. proposed a flow chart to determine the risk of developing arrhythmic complications for the oncologic patients undergoing targeted therapies treatment [65].
For an optimal management of QT prolongation, we believe it is necessary to maximize the prevention, optimize the QT interval measurements and modify and/or discontinue the therapy in relation to the degree of QT lengthening. We think that a specific algorithm for each drug or family drug could be particularly useful. These algorithms should contain information on management on the basis of the presence of correctable factors, for example: electrolyte imbalance, hypothyroidism, and concurrent use of QT prolonging drug.
Finally, the management of major arrhythmias and TdP should be handled by cardiologists or intensivists who are aware of cancer drugs metabolism and half-life.

Conflict of interest

The authors declare no conflict of interest.

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Author contribution

Conception/Design: Nicola Maurea
Data analysis and interpretation: Nicola Maurea and Carmela Coppola
All the authors contributed to the preparation of the manuscript. The final version of the manuscript has been read and approved by all the authors before its submission.

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Bibliography

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[1] Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol 2014; 64:938–945.
[2] Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. J Clin Oncol 2007;25:3362–3371.
[3] Taran LM, Szilagyi N. The duration of the electrical systole (Q-T) in acute rheumatic carditis in children.Am Heart J 1947;33:14 –26.
[4] Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. 1920. Ann Noninvasive Electrocardiol 2003;8:343–351.
[5] Sagie A, Larson MG, Goldberg RJ et al. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992;70:797– 801.
[6] Desai M, Li L, Desta Z et al. Variability of heart rate correction methods for the QTinterval. Br J Clin Pharmacol 2003;55:511–517.
[7] Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Available at: http://www.fda.gov/downloads/Regulatory/Information/Guidances/ucm129357.pdf.Accessed May 13, 2013.
[8] National Cancer Institute. Common Terminology Criteria for Adverse Events v 4.0. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010 – 06-14_QuickReference_8.5x11.pdf.Accessed May 13, 2013.
[9] Brell JM. Prolonged QTc interval in cancer therapeutic drug development: Defining arrhythmic risk in malignancy. Prog Cardiovasc Dis 2010;53:164–172.
Anderson ME, Al-Khatib SM, Roden DM et al. Cardiac repolarization: Current knowledge, critical gaps, and new approaches to drug development and patient management. Am Heart J 2002;144:769–781.
[10] Nielsen J, Graff C, Kanters JK et al. Assessing QT interval prolongation and its associated risks with antipsychotics. CNS Drugs. 2011;25:473-490.
[11] Li EC, Esterly JS, Pohl S et al. Drug-induced QT-interval prolongation: considerations for clinicians.Pharmacotherapy. 2010;30:684-701.
[12] Edward T.H. Yeh. Onco-Cardiology. The Time Has Come. Tex Heart Inst J. Cancer and the Heart 2011; 38(3): 246–247.
[13] CredibleMeds QT drugs list website sponsored by Science Foundation of the University of Arizona. Available at http://crediblemeds.org/.
[14] Maurea N, Spallarossa P, Cadeddu C, *et al*. A recommended practical approach to the management of target therapy and angiogenesis inhibitors cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology. J Cardiovasc Med (Hagerstown). 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e93-e104.
[15] Hasinoff BB. The cardiotoxicity and myocyte damage caused by small molecule anticancer tyrosine kinase inhibitors is correlated with lack of target specificity. Toxicol Appl Pharmacol. 2010;244:190-195.
[16] Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). Drug Saf 2013;36:295-316.
[17] Ghatalia P, Je Y, Kaymakcalan MD, Sonpavde G et al. QTc interval prolongation with vascular endothelial growth factor receptor tyrosine kinase inhibitors. Br J Cancer 2015; 112:296-305.
[18] Lu Z, Wu CY, Jiang YP, et al. Suppression of phosphoinositide 3-kinase signaling and alteration of multiple ion currents in drug-induced long QT syndrome. Sci Transl Med. 2012 Apr 25;4(131):131ra50
[19] Ghatalia P, Je Y, Kaymakcalan MD, et al. QTc interval prolongation with vascular endothelial growth factor receptor tyrosine kinase inhibitors. Br J Cancer. 2015 Jan 20;112(2):296-305.

ACCEPTED MANUSCRIPT

[20] US FDA drug approval summary for vandetanib in medullary thyroid cancer available online at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022405s000lbl.pdf (Accessed on April 25, 2011.
[21] Zang J, Wu S, Tang L, et al. Incidence and risk of QTc interval prolongation among cancer patients treated with vandetanib: a systematic review and meta-analysis. PLoS One 2012; 7:e30353.
[22] FDA-approved manufacturer's package insert for vandetanib available online at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=4dc7f0af-77fb-4eec-46b9-dd1c2dcb4525 (Accessed on January 25, 2013).
[23] Cook KM, Figg WD. Angiogenesis inhibitors: current strategies and future prospects. CA Cancer J Clin. 2010;60:222-243.
[24] Hurwitz HI, Dowlati A, Saini S et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. 2009;15:4220-4227.
[25] Hutson TE, Davis ID, Machiels JP et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2010;28:475-480.
[26] Heath EI, Infante J, Lewis LD et al. A randomized, double-blind, placebo-controlled study to evaluate the effect of repeated oral doses of pazopanib on cardiac conduction in patients with solid tumors. Cancer Chemother Pharmacol. 2013;71:565-573.
[27] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356:115-124.
[28] Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125-134.
[29] Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008; 26:5204-5212.
[30] Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011-2019.
[31] Girardi F, Franceschi E, Brandes AA. Cardiovascular safety of VEGF-targeting therapies: current evidence and handling strategies. Oncologist. 2010; 15:683-694.
[32] Lenihan DJ, Kowey PR. Overview and management of cardiac adverse events associated with tyrosine kinase inhibitors. Oncologist. 2013; 18(8):900-8.
[33] Bello CL, Mulay M, Huang X, et al. Electrocardiographic characterization of the QTc interval in patients with advanced solid tumors: pharmacokinetic- pharmacodynamic evaluation of sunitinib. Clin Cancer Res 2009; 15:7045-7052.
[34] Hutson TE, Figlin RA, Kuhn JG et al. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. Oncologist. 2008;13:1084-1096.
[35] Tolcher AW, Appleman LJ, Shapiro GI, et al. A phase I open-label study evaluating the cardiovascular safety of sorafenib in patients with advanced cancer. Cancer Chemother Pharmacol 2011; 67:751-764.
[36] http://www.agenziafarmaco.gov.it
[37] Lee HA, Kim EJ, Hyun SA et al. Electrophysiological effects of the anti-cancer drug lapatinib on cardiac repolarization. Basic Clin Pharmacol Toxicol. 2010; 107:614-618.
[38] Rios MB1, Ault P. Identification of side effects associated with intolerance to BCR-ABL inhibitors in patients with chronic myeloid leukemia. Clin J Oncol Nurs. 2011; Dec;15(6):660-7.
[39] Bristol-Myers Squibb Company: Sprycel (dasatinib) prescribing information. Princeton, NJ 2006.
[40] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=32204&CFID=11456208&CFTOKEN=1f74eda9f81e615f-6771DE68-92AA-956A3738E4B0F5A05DA7&jsessionid=ca30878ec315457e3b38 (Accessed on November 22, 2010).
[41] Mann BS, Johnson JR, He K et al. Vorinostat for treatment of cutaneous manifestations of advanced primary cutaneous T-cell lymphoma. Clin Cancer Res. 2007;13:2318-2322.

ACCEPTED MANUSCRIPT

[42] Woo S, Gardner ER, Chen X et al. Population pharmacokinetics of romidepsin in patients with cutaneous T-cell lymphoma and relapsed peripheral T-cell lymphoma. Clin Cancer Res. 2009;15:1496-1503.
[43] Piekarz RL, Frye AR, Wright JJ, et al. Cardiac studies in patients treated with depsipeptide, FK228, in a phase II trial for T-cell lymphoma. Clin Cancer Res 2006; 12:3762-3773.
[44] Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007; 25:3109-3115.
[45] Shah MH, Binkley P, Chan K, et al. Cardiotoxicity of histone deacetylase inhibitor depsipeptide in patients with metastatic neuroendocrine tumors. Clin Cancer Res 2006; 12:3997-4003.
[46] Bailey H, Stenehjem DD, Sharma S. Panobinostat for the treatment of multiple myeloma: the evidence to date J Blood Med. 2015;6:269-276.
[47] Doyle AC. Notes of a case of leukocythaemia. Lancet 1882; 119: 490.
[48] Forkner CE, Scott TF. Arsenic as a therapeutic agent in chronic myelogenous leukemia. JAMA 1931; 97:3–5.
[49] Ghavamzadeh A, Alimoghaddam K, Ghaffari SH et al. Treatment of acute promyelocytic leukemia with arsenic trioxide without ATRA and/or chemotherapy. Ann Oncol 2006; 17:131–134.
[50] Mathews V, George B, Kavitha M, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity. Blood 2006; 107:2627–2632.
[51] Goldsmith S, From AH. Arsenic-induced atypical ventricular tachycardia. N Engl J Med 1980;303:1096-1098.
[52] Little RE, Kay GN, Cavender JB et al. Torsade de pointes and T-U wave alternans associated with arsenic poisoning. Pacing Clin Electrophysiol 1990;13:164-170.
[53] St Petery J, Gross C, Victorica BE. Ventricular fibrillation caused by arsenic poisoning. Am J Dis Child 1970;120:367-371.
[54] Weinberg SL. The electrocardiogram in acute arsenic poisoning. Am Heart J 1960;60:971-975.
[55] Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. J Clin Oncol. 2003;21:3609-3615.
[56] Drolet B, Simard C, Roden DM. Unusual effects of a QT-prolonging drug, arsenic trioxide, on cardiac potassium currents. Circulation. 2004;109:26-29.
[57] Lane AA, Chabner BA. Histone deacetylase inhibitors in cancer therapy. J Clin Oncol 2009; 27:5459-5468.
[58] Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011; 364:2507-2516.
[59] Shaw AT, Kim DW, Mehra R et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014;370:1189-1197.
[60] Wei H, Du F, Lu Y, Wei J, Dong X. Successful ceritinib treatment in a man with MPE and an ALK fusion gene mutation after multiple treatments. Springerplus. 2016 Dec 7;5(1):2083.
[61] Ou SH, Tong WP, Azada M et al. Heart rate decrease during crizotinib treatment and potential correlation to clinical response. Cancer. 2013;119:1969-1975
[62] Charlotte van Noord, Mark Eijgelsheim, and Bruno H Ch Stricker. Drug- and non-drug-associated QT interval prolongation. Br J Clin Pharmacol. 2010 Jul; 70(1): 16–23.
[63] Agrawal S, Waxman I, Lambert A, et al. Cancer Chemother Pharmacol. Evaluation of the potential for QTc prolongation in patients with solid tumors receiving nivolumab. 2016 Mar;77(3):635-41

ACCEPTED MANUSCRIPT

[64] Diemberger I, Massaro G, Cubelli M, *et al*. Repolarization effects of multiple-cycle chemotherapy and predictors of QTc prolongation: a prospective female cohort study on >2000 ECGs. Eur J Clin Pharmacol. 2015 Aug;71(8):1001-9.

[65] Cuni R, Parrini I, Asteggiano R, Conte MR.c Targeted Cancer Therapies and QT Interval Prolongation: Unveiling the Mechanisms UnderlyingArrhythmic Complications and the Need for Risk Stratification Strategies. Clin Drug Investig. 2017 Feb;37(2):121-134.

[66] Chalmers AJ. The potential role and application of ParP inhibitors in cancer treatment. Br Med Bull. 2009; 89:23–40

[67] Kaufman B, Shapira-Frommer R, Schmutzler RK, *et al.* Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244–250.

[68] Dockery LE, Gunderson CC, and Moore KN. Rucaparib: the past, present, and future of a newly approved PARP inhibitor for ovarian cancer. Onco Targets Ther. 2017; 10: 3029–3037.

[69] Balasubramaniam S, Beaver JA, Horton S, *et al.* FDA Approval Summary: Rucaparib for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer. Clin Cancer Res. 2017 Jul 27.

[70] Caruso D, Papa A, Tomao S, *et al.* Niraparib in ovarian cancer: results to date and clinical potential. Ther Adv Med Oncol. 2017 Sep;9(9):579-588.

[71] Mirza MR, Monk BJ, Herrstedt J, *et al.* Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164.

[72] Munasinghe W, Stodtmann S, Tolcher A, *et al.* Effect of veliparib (ABT-888) on cardiac repolarization in patients with advanced solid tumors: a randomized, placebo-controlled crossover study. Cancer Chemother Pharmacol. 2016 Nov;78(5):1003-1011.

[73] Plummer R1, Stephens P, Aissat-Daudigny L, *et al.* Phase 1 dose-escalation study of the PARP inhibitor CEP-9722 as monotherapy or in combination with temozolomide in patients with solid tumors. Cancer Chemother Pharmacol. 2014 Aug;74(2):257-65.

[74] Ledermann J, Harter P, Gourley C, *et al*. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014 Jul;15(8):852-61.

[75] E Pujade-Lauraine *et al.* Olaparib Tablets as Maintenance Therapy in Patients With Platinum-Sensitive, Relapsed Ovarian Cancer and a BRCA1/2 Mutation (SOLO2/ENGOT-Ov21): A Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trial. Lancet Oncol 18 (9), 1274-1284. 2017 Jul 25.

[76] Tutt A, Robson M, Garber JE, *et al.* Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010 Jul 24;376(9737):235-44.

[77] Swaisland H, Plummer R, So K, *et al*. Olaparib does not cause clinically relevant QT/QTc interval prolongation in patients with advanced solid tumours: results from two phase I studies. Cancer Chemother Pharmacol. 2016 Oct;78(4):775-84.

ACCEPTED MANUSCRIPT

[78] Doi T, Hewes B, Kakizume T, et al. A Phase 1 Study of Single-Agent Ribociclib in Japanese Patients With Advanced Solid Tumors. Cancer Sci. 2017 Oct 23.

[79] Sonke GS, Hart LL, Campone M, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2017 Oct 22.

[80] Therapy Management Guide-Kisqali (Ribociclib) NOVARTIS 2017

[81] "FDA Approves Palbociclib for Metastatic Breast Cancer". OncLive. 3 Feb 2015.

[82] "Pfizer Receives U.S. FDA Accelerated Approval of IBRANCE (palbociclib)". Pfizer. 3 Feb 2015.

[83] Bell T, Crown JP, Lang I, et al. Impact of palbociclib plus letrozole on pain severity and pain interference with daily activities in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer as first-line treatment. Curr Med Res Opin. 2016 May;32(5):959-65.

[84] Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35.

[85] Data on file. Pfizer Inc, New York, NY.

[86] Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375(20):1925-1936.

[87] Spring LM, Zangardi ML, Moy B and Bardia A. Clinical Management of Potential Toxicities and Drug Interactions Related to Cyclin-Dependent Kinase 4/6 Inhibitors in Breast Cancer: Practical Considerations and Recommendations. Oncologist. 2017 Sep;22(9):1039-1048.

[88] Kim ES, Scott LJ. Palbociclib: A Review in HR-Positive, HER2-Negative, Advanced or Metastatic Breast Cancer. Target Oncol. 2017 Jun;12(3):373-383.

[89] Ibrance (palbociclib) European public assessment report.

[90] Loibl S, Turner NC, Ro J, et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. Oncologist. 2017 Sep;22(9):1028-1038.

[91] Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016 Apr;17(4):425-39.

[92] Niesvizky R, Badros AZ, Costa LJ, et al. Phase 1/2 study of cyclin-dependent kinase (CDK)4/6 inhibitor palbociclib (PD-0332991) with bortezomib and dexamethasone in relapsed/refractory multiple myeloma. Leuk Lymphoma. 2015;56(12):3320-8.

[93] Schwartz GK, LoRusso PM, Dickson MA, et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). Br J Cancer. 2011 Jun 7;104(12):1862-8.

ACCEPTED MANUSCRIPT

[94] Flaherty KT, Lorusso PM, Demichele A, et al. Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. Clin Cancer Res. 2012 Jan 15;18(2):568-76.

[95] Barroso-Sousa R, Shapiro GI, Tolaney SM. Clinical Development of the CDK4/6 Inhibitors Ribociclib and Abemaciclib in Breast Cancer. Breast Care (Basel). 2016 Jun;11(3):167-73.

[96] Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer. Clin Cancer Res. 2017 Sep 1;23(17):5218-5224.

[97] Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017 Sep 1;35(25):2875-2884.

Figure Caption

Fig.1 Correction formulas to improve QT measurement.
Fig.2 Tangent method for QT interval measurement.
Fig.3 Assessment and management scheme in course of chemotherapy with potential QTc effect.
Fig.4 QT monitoring during lapatinib.
Fig.5 Algorithm for the management of QT prolongation induced by panobinostat.
Fig.6 QT monitoring during crizotinib.

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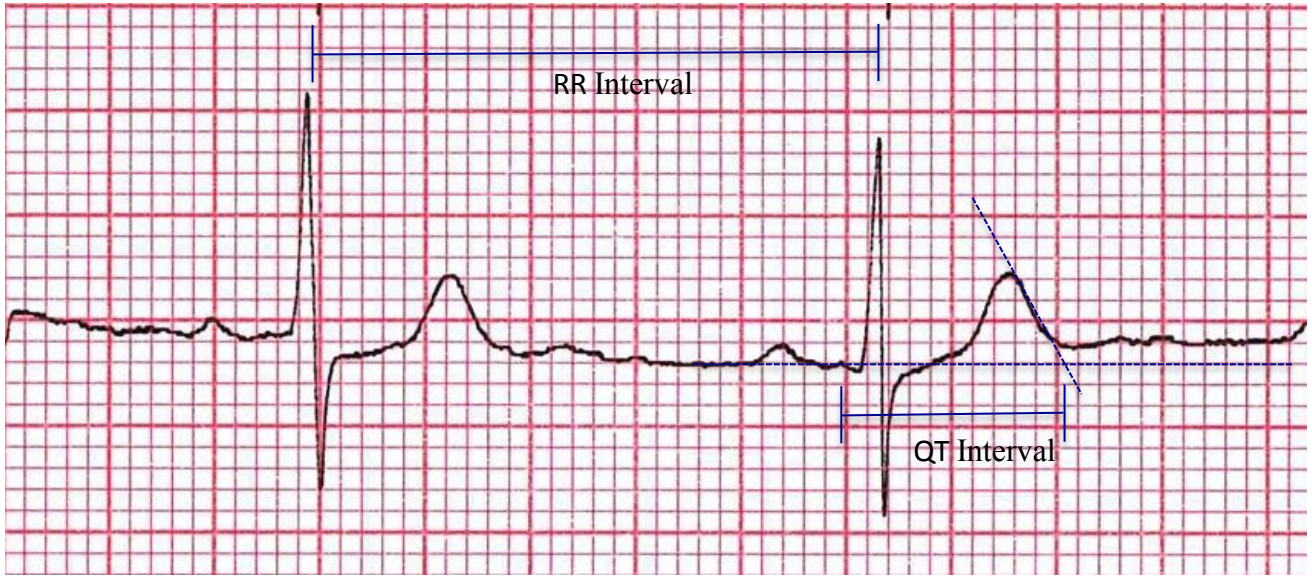
Figure(s)

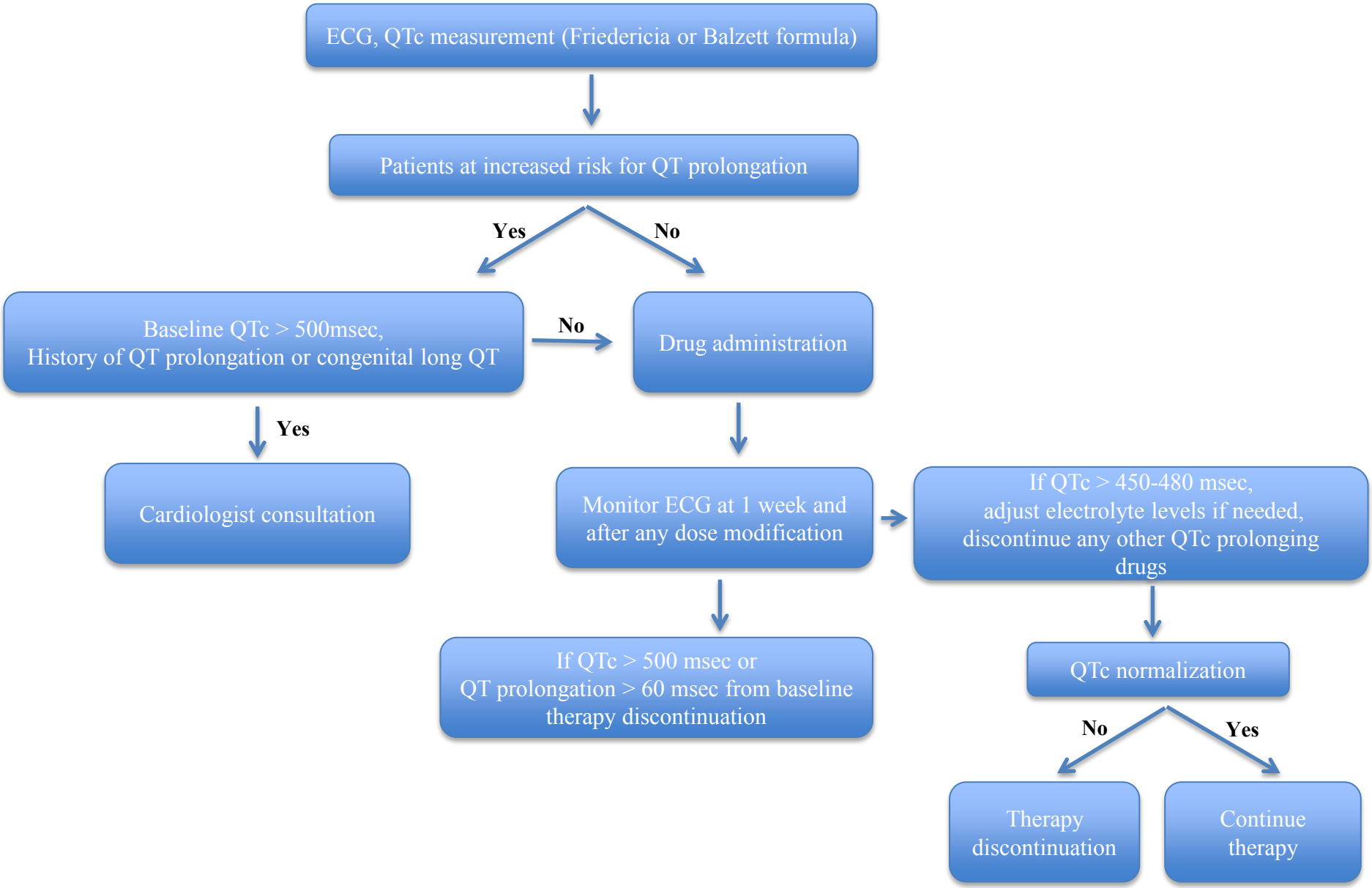
$$QTc = \frac{QT}{\sqrt{RR}}$$ **Balzett**

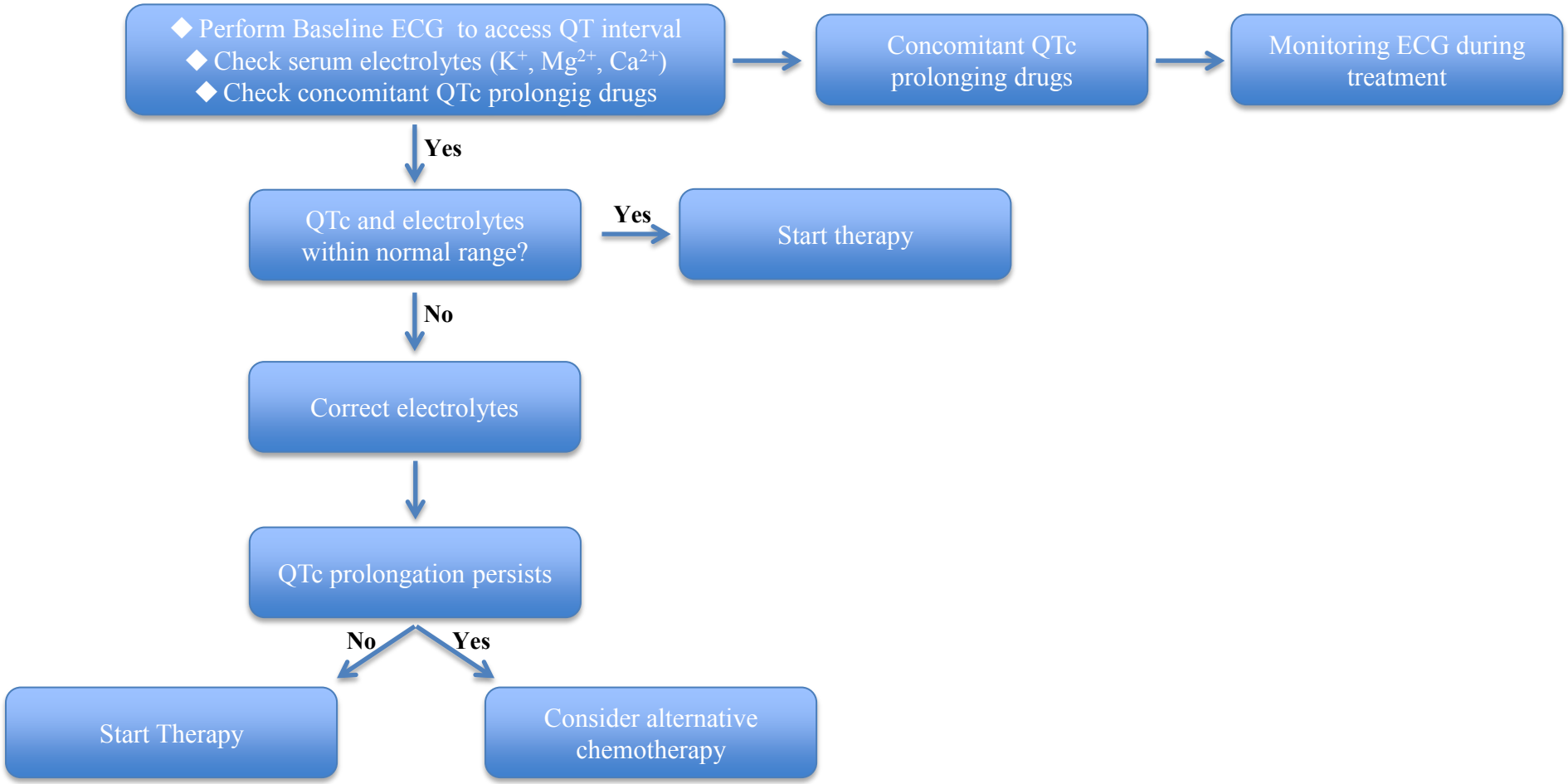
$$QTc = RR^{1/3}$$ **Fredericia**

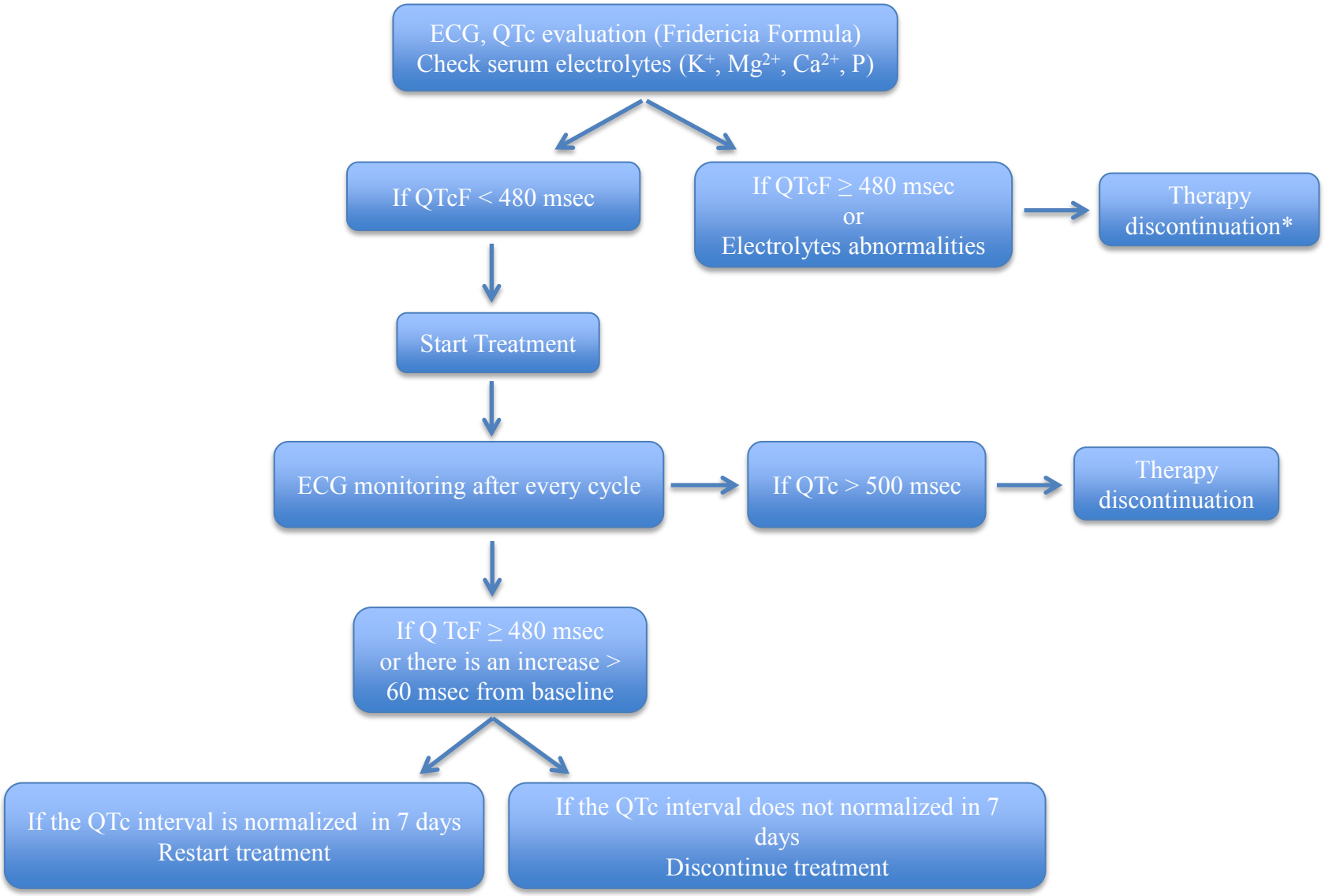
$$QTc = QT + 0{,}154(1 - RR)$$ **Framingham**

$$QTc = QT + 1{,}75(Fc - 60)$$ **Hodges**

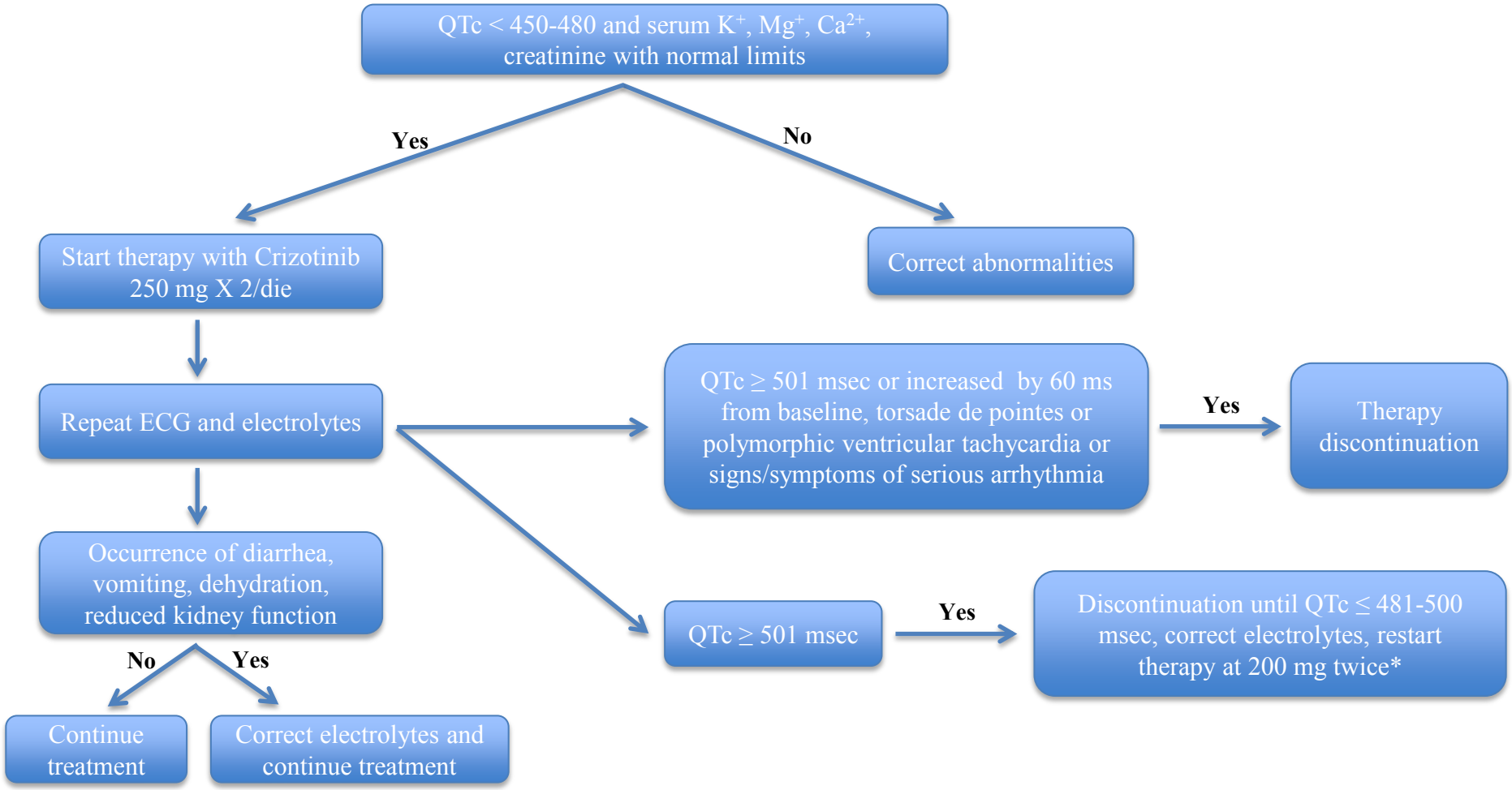

RR Interval
QT Interval


ECG, QTc measurement (Friedericia or Balzett formula)
Patients at increased risk for QT prolongation
Yes
No
Baseline QTc > 500msec,
History of QT prolongation or congenital long QT
No
Drug administration
Yes
Cardiologist consultation
Monitor ECG at 1 week and
after any dose modification
If QTc > 450-480 msec,
adjust electrolyte levels if needed,
discontinue any other QTc prolonging
drugs
If QTc > 500 msec or
QT prolongation > 60 msec from baseline
therapy discontinuation
QTc normalization
No
Yes
Therapy
discontinuation
Continue
therapy


◆ Perform Baseline ECG to access QT interval
◆ Check serum electrolytes (K^+, Mg^{2+}, Ca^{2+})
◆ Check concomitant QTc prolongig drugs
Concomitant QTc prolonging drugs
Monitoring ECG during treatment
Yes
QTc and electrolytes within normal range?
Yes
Start therapy
No
Correct electrolytes
QTc prolongation persists
No
Yes
Start Therapy
Consider alternative chemotherapy



* Treatment must not be started until QTcF < 480 msec and/or electrolytes have been corrected.



*In case of further appearance of toxicity CTCAE grade > 3, permanently discontinue treatment.

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- Although the recent progresses of cancer therapies have significantly improved the prognosis of oncologic patients, side effects of antineoplastic treatments are still responsible for the high mortality of cancer survivors.

- Cardiovascular toxicity is the most dangerous adverse effect induced by anticancer therapies.

- Although the incidence of QT prolongation induced by drugs is generally low, it is one of the cardiovascular complications that oncologists and cardiologists have to deal with.

- The management of major arrhythmias and TdP should be handled by cardiologists or intensivists who are aware of cancer drugs metabolism and half-life.

The authors declare no conflict of interest.

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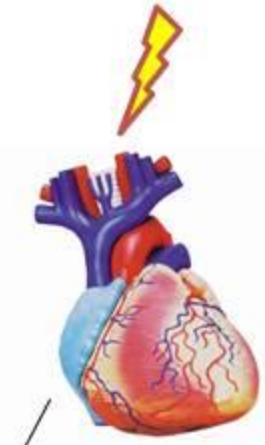
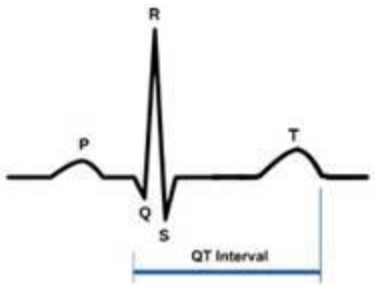
Antineoplastic drugs
Target therapy

Cardiotoxic effects



Long-QT



Tumor cells