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Current Perspective

Current perspective: Osimertinib-induced QT prolongation: new drugs with new side-effects need careful patient monitoring

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Abstract An increasing number of tyrosine kinase inhibitors (TKIs) are available for the treatment of non–small cell lung cancer (NSCLC). QT prolongation is one of the known, but relatively rare, adverse events of several TKIs (e.g. osimertinib, crizotinib, ceritinib). Screening for QT prolongation in (high risk) patients is advised for these TKIs. When a QT prolongation develops, the physician is challenged with the question whether to (permanently) discontinue the TKI. In this perspective, we report on a patient who developed a grade III QT prolongation during osimertinib (a third-generation epidermal growth factor receptor [EGFR]-TKI) treatment. On discontinuation of osimertinib, she developed a symptomatic disease flare, not responding to subsequent systemic treatment. The main aim of this perspective is to describe the management of QT prolongation in stage IV *EGFR* driver mutation NSCLC patients. We also discuss the ethical question of how to weigh the risk of a disease flare due to therapy cessation against the risk of sudden cardiac death. A family history of sudden death and a prolonged QT interval might indicate a familiar long QT syndrome. We have summarised the current monitoring advice for TKIs used in the treatment of lung cancer and the most common drug–TKI interactions to consider and to optimise TKI treatment in lung cancer patients.

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1. Introduction

More and more targetable molecular drivers of non-small cell lung cancer (NSCLC) are being discovered [1]. The targeted agents for these driver mutations are often tyrosine kinase inhibitors (TKIs). The European Medicines Agency (EMA)- and US Food and Drug Administration (FDA)–approved TKIs for activating epidermal growth factor receptor (*EGFR*) mutations include erlotinib, gefitinib, afatinib and osimertinib. Examples of TKIs approved for anaplastic lymphoma kinase rearrangements are crizotinib, ceritinib and alectinib and for *ROS1* translocations, crizotinib is approved [1]. *EGFR* mutations are found in approximately 10–15% of Caucasian patients with stage IV non-squamous NSCLC [2], and this percentage increases to more than 60% in non-smoking Asian females [3]. An activating *EGFR* mutation is predictive for response to EGFR-TKI [4]. For example, osimertinib is a third-generation EGFR-TKI and EMA approved for *EGFR*-mutated patients with a T790M mutation. Recently, results of the first line randomised phase III

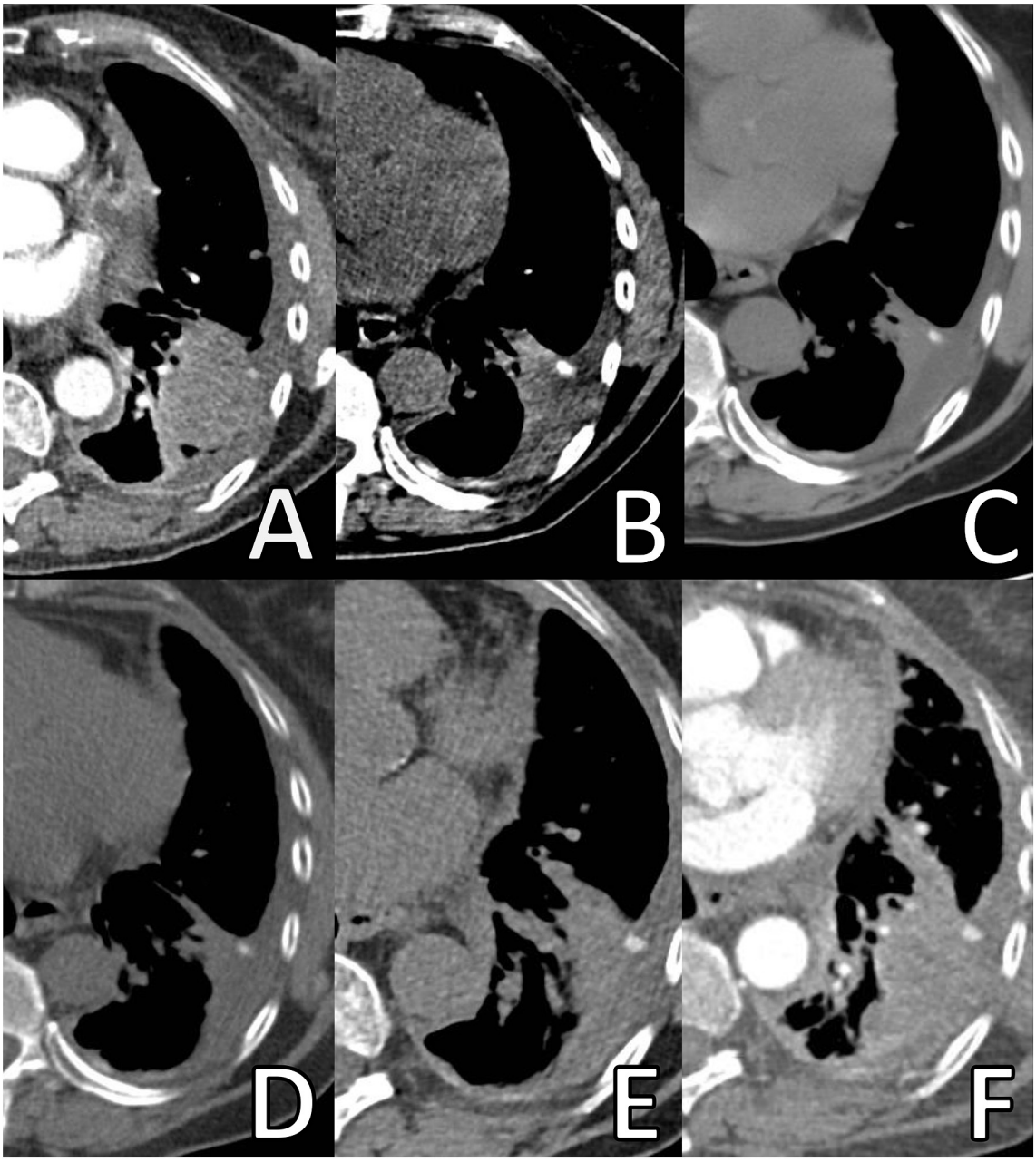

Fig. 1. Primary tumour in the left lower lobe before, during and after osimertinib therapy. Consecutive CT scans demonstrating the primary tumour in the left lower lobe, adjacent to a pleural thickening and calcification caused by previous empyema. (A) Before osimertinib therapy. (B) Day 32 of osimertinib therapy, partial response. (C) Day 183, stable situation. (D) Day 241, slow progression. (E) Day 301, slow progression. (F) Day 350, rapid progression after cessation of osimertinib. CT, computed tomography.

FLAURA trial were reported, and it was shown that osimertinib had a superior progression free survival (PFS) compared with gefitinib [5]. For osimertinib, most common adverse events (almost all grade I or II) are diarrhoea (41%), rash (34%), dry skin (23%) and paronychia (22%). Although not frequent, QT prolongation is one of the known adverse events, and this occurs in approximately 4% of patients (almost all patients grade I or II) [6]. For several other TKIs, QT prolongation has been described [7–10]. For a grade III QT prolongation, it is advised to temporarily discontinue the causative agent as there is an increased risk of sudden cardiac death due to ventricular tachycardia and torsade de pointes [11]. However, discontinuation of a TKI can result in a rapid symptomatic disease flare [12]. In the case reported below, we discuss that a disease flare due to therapy cessation should be weighed against the risk of sudden cardiac death. Furthermore, we provide recommendations for QT management in a patient treated with a TKI. In a broader perspective, we summarise the current monitoring advice for TKIs (almost) approved for the treatment of lung cancer and the most common drug–TKI interactions to consider and to optimise TKI treatment of lung cancer patients.

1.1. Case report

A 62-year-old female known with stage IV pulmonary adenocarcinoma with an *EGFR* exon 19 deletion was treated with fourth line osimertinib 80 mg once daily. This was well tolerated and resulted in a rapid clinical and radiological response. After 9 months, a very slow asymptomatic progression was observed (Fig. 1); osimertinib was continued because of persisting clinical benefit. Regular (2 weekly) electrocardiograms (ECGs) were performed for the first 2 months, thereafter monthly. These ECGs showed no abnormalities. However, after 11 months, there was a sudden grade III QT prolongation (560 ms) (Fig. 2). Electrolytes were normal; no other QT-prolonging drugs were used. Osimertinib was discontinued, and on advice of the cardiologist, a detailed family history was obtained. A brother and uncle had sudden cardiac deaths. Because of the family history, the patient was referred for genetic counselling for a workup of familial QT prolongation. Genetic counselling showed no specific mutations related to the long QT syndrome (no pathogenic mutations in KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ8, CAV3, KCNJ2 and exon 8 of the CACNA1C gene) [13,14]. Within 5 days, the QT interval normalised, and osimertinib was not reintroduced because of the already occurring slow progressive disease. A new tumour biopsy was performed directly after discontinuing osimertinib. Within 2 weeks of discontinuing osimertinib, while awaiting biopsy results, a rapid symptomatic disease progression occurred, not responding to fifth line pemetrexed monotherapy. Biopsy results became available during pemetrexed treatment but revealed no druggable target and no T790M. The patient died from symptomatic brain metastasis 2 months after discontinuation of osimertinib.

1.2. Discussion: monitoring of TKI treatment

For several TKIs, grade III or higher QT prolongation has been described (e.g. osimertinib: 1%, dacomitinib: 1%, crizotinib: 3%, ceritinib: 3–6%) [7–10]. Animal models suggest that this is caused by inhibition of PI3K signalling [15]. QT prolongation has been reported in 4% of patients receiving osimertinib and was classified a

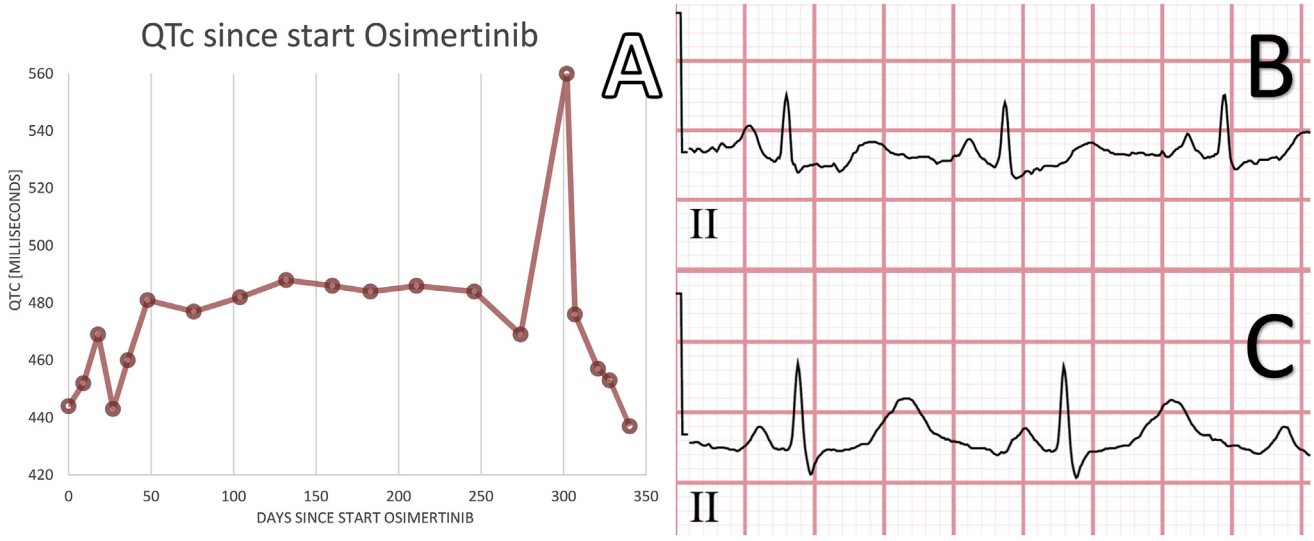

Fig. 2. QT interval during osimertinib therapy. (A) Graphic presentation of the development of corrected QT time during and after osimertinib therapy, which was discontinued at day 302. (B) Electrocardiogram (ECG) at the start of osimertinib therapy, demonstrating a QTc of 444 ms. (C) ECG at day 302 of osimertinib therapy, demonstrating a QTc of 560 ms.

Table 1
Summary of advised monitoring per TKI.

Monitoring	Renal function & electrolytes[c]	Liver function[c]	Fasting plasma glucose[c]	Creatine kinase,[d] myalgia symptoms	Pancreatic enzymes	Lipid profile[d]	Blood count and differentiation	Close INR control in coumarin therapy	Pulse and blood pressure	ECG (in patients at risk)	Echocardiography (in patients at risk)	ILD symptoms	Ocular symptoms	Bullous skin conditions	Heart failure symptoms
Gefitinib (Iressa) [20]	x	x						x				x	x		
Erlotinib (Tarceva) [21]	x	x						x				x	x	x	
Afatinib (Giotrif) [22]	x	x									x	x	x	x	x
Dacomitinib[a] (PF-00299804) [23]	x	x					x			x	x	x	x		X[b]
Osimertinib (Tagrisso) [11]	x	x								(x)	x	x	x		x
Crizotinib (Xalkori) [16]	x	x					x		x	x	x	x	x		x
Ceritinib (Zykadia) [17]	x	x	x		x[e]				x	x		x			x
Alectinib (Alecensa) [24]	x	x		x					x			x			
Brigatinib (Alunbrig) [25]	x	x	x	x	x[c]				x			x	x		
Lorlatinib[a] (PF-6463922) [26]	x	x			x[d]	x	x	x		x		x			

INR, international normalized ratio; ECG, electrocardiogram; ILD, interstitial lung disease; TKI, tyrosine kinase inhibitor; FDA, US Food and Drug Administration; EMA, European Medicines Agency.

[a] Not yet FDA or EMA approved.

[b] Preclinical toxicology studies did not show cardiotoxicity.

[c] At baseline, monthly and as clinically indicated in patients reporting symptoms.

[d] At baseline, every two weeks during the first month of treatment and as clinically indicated in patients reporting symptoms.

[e] At baseline and as clinically indicated in patients reporting symptoms.

grade III adverse event in 1%. Although the QT prolongation is rare, for osimertinib, it is advised to regularly perform an ECG in patients at risk for QT prolongation [11]. For crizotinib and ceritinib, it is advised to perform baseline ECGs in all patients and regular ECGs at least in patients at risk for QT prolongation [16,17]. As the TKIs used in the treatment of driver mutated NSCLC differ in their adverse event profile, monitoring of patients should be tailored according to the prescribed TKI. Furthermore, interaction with other drugs can cause an increase or decrease in the plasma concentration of the TKI, resulting in a higher chance of adverse events or in possible undertreatment of the patient. Monitoring advice is summarised in Table 1, and possible drug–TKI interactions with the resulting effects on the TKI are presented in Table 2.

A prolonged QT interval can lead to ventricular tachycardia and torsade de pointes with potentially fatal outcome. It can present as a congenital 'long QT syndrome' and can be provoked by conditions such as bradycardia or hypokalemia or exposure to certain drugs. In general, a QT prolongation beyond 500 ms should prompt cessation of QT-prolonging drugs to prevent sudden cardiac death as the relative risk of a cardiac death is more than 2.5 times that of a person without QT prolongation [14,18]. Predisposing factors for QT prolongation and their risk management are summarised in Table 3.

In our case, the risk of fatal arrhythmia due to QT prolongation occurred in the context of a stage IV *EGFR*-mutated pulmonary adenocarcinoma that was treated with an EGFR-TKI. Disease flare after TKI discontinuation has been described and occurred after a median of 8 days [12]. This unfavourable prognostic consequence of therapy cessation should be weighed against the risk of sudden cardiac death. An ethical question is whether a risk of iatrogenic death is acceptable in palliative oncologic therapy. In case of therapy continuation, preventive measures to limit the risk of cardiac arrhythmias consist of early patient reporting of palpitations and (near) syncope, early recognition and treatment of hypokalemia, beta-blocker therapy and avoidance of concomitant QT-prolonging or interacting drugs (Table 3) [13,14]. Furthermore, attention should be paid to the family history as a prolonged QT interval might indicate a familial long QT syndrome [13,14]. When there is an indication for a familial long-QT syndrome, first degree family members with a (suspicion of) a long-QT syndrome are eligible for a periodical cardiology evaluation [19]. In general, one should be aware of the monitoring advice for TKI use and possible drug–TKI interactions to optimise the TKI treatment of lung cancer patients.

At this point, we do not know if dose reduction is associated with a decreased risk of QT prolongation or if QT prolongation would recur or not with the introduction of a lower dose. However, as our patient already

Table 2
Summary of important drug interactions per TKI.

Type of drug	CYP3A4 inhibitors[b]	CYP3A4 inducers[c]	CYP1A2 inhibitors[d]	P-gp inhibitors[e]	P-gp inducers[f]	P-gp–dependent drugs[g]	BCRP-dependent drug[h]	CYP3A-dependent drugs[i]	CYP2C9-dependent drugs[j]	CYP2B6-dependent drugs[k]	CYP2D6-dependent drugs[l]	QT-prolonging drugs[m]	Gastrointestinal toxic drugs	Hepatotoxic drugs	Gastric pH–modifying agents	Coumarins (INR increase)	Statins (myopathy risk)	Oral contraception unsafe
Gefitinib (Iressa) [20]	x	x	x								x				x	x		
Erlotinib (Tarceva) [21]	x	x	x	x									x			x	x	
Afatinib (Giotrif) [22]				x	x		x											
Dacomitinib[a] (PF-00299804) [23]						x					x	x		x				
Osimertinib (Tagrisso) [11]		x					x					x						x
Crizotinib (Xalkori) [16]	x	x				x		x		x		x	x	x				x
Ceritinib (Zykadia) [17]	x	x		x	x	x	x					x			x			
Alectinib (Alecensa) [24]						x	x											x
Brigatinib (Alunbrig) [25]	x	x						x										
Lorlatinib[a] (PF-6463922) [26]	x	x				x		X[n]	x	x						x		

FDA, US Food and Drug Administration; TKI, tyrosine kinase inhibitor; EMA, European Medicines Agency.

[a] Not yet FDA or EMA approved.

[b] CYP3A4-inhibiting drugs increase TKI concentration, i.e. grapefruit juice, azoles, erythromycin, clarithromycin, boceprevir and HIV protease inhibitors.

[c] CYP3A-inducing drugs decrease TKI concentration, i.e. phenytoin, rifampicin, carbamazepine, barbiturates and St. John's wort.

[d] CYP1A2 inhibitors increase TKI concentration, i.e. ciprofloxacin and fluvoxamine.

[e] P-glycoprotein inhibitors increase TKI concentration, i.e. oritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir and amiodarone.

[f] P-glycoprotein inducers decrease TKI concentration, i.e. rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's wort.

[g] P-glycoprotein–dependent drugs increase in plasma concentration, i.e. digoxin, colchicine, dabigatran, paclitaxel, pravastatin and vincristine.

[h] Breast cancer resistance protein BCRP)–dependent drugs increase in plasma concentration, i.e. rosuvastatin, methotrexate, sulfasalazine and topotecan.

[i] CYP3A-dependent drugs increase in plasma concentration, i.e. astemizole, cisapride, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus.

[j] CYP2C9-dependent drugs increase in plasma concentration, i.e. phenytoin and warfarin.

[k] CYP2B6-dependent drugs increase in plasma concentration, i.e. bupropion and efavirenz.

[l] CYP2D6-dependent drugs increase in plasma concentration, i.e. metoprolol.

[m] QT-prolonging drugs, i.e. amiodarone, kinidine, disopyramide, sotalol, domperidone, methadone, tricyclic antidepressants, antipsychotics, macrolide antibiotics, fluorchinolones, antimycotics, granisetron and ondansetron.

[n] CYP3A-dependent drugs decrease in plasma concentration.

Table 3
Risk factors and preventive measures regarding drug-induced QT prolongation.

Predisposing factors for QT prolongation	Risk management
Electrolyte disturbances (hypoK, −Mg, −Ca)	Laboratory monitoring (in vomiting, diarrhoea) Caution using provoking drugs (i.e. diuretics)
Provoking or interacting drugs	Pharmacologic surveillance; drug avoidance Regular ECGs; screening for gene polymorphisms
Heart failure, left ventricular hypertrophy, extreme bradycardia	Cardiologic screening and optimalisation ECG monitoring
Strenuous physical activity, hypothermia	Avoidance, patient education
Hypothyroidism	Laboratory screening and suppletion
Female sex, increasing age	Awareness
Family history LQT syndrome, sudden death	Awareness Genetic counselling

hypoK, hypokaliemia; Mg, magnesium; Ca, calcium; ECG, electrocardiogram; LQT, long QT.

had progressive disease on full dose osimertinib, we did not think that a lower dose would give us disease control or a reassurance about the effect on the QT interval.

2. Conclusion

New drugs have new side-effects that require more general medical input, often in the course of a busy oncology clinic. We think that a prolonged QT interval due to palliative cancer therapy should not automatically result in therapy cessation, but should be weighed against the risk of disease flare. Genetic testing should be considered especially with a family history of sudden death.

We have developed some tables that should help busy clinicians to make decisions.

Conflict of interest statement

None declared.

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