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Complications of Treatment

Drug-drug interactions in breast cancer patients treated with CDK4/6 inhibitors

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ABSTRACT

CDK4/6 inhibitors are a new class of anticancer drugs used for the treatment of women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. Polypharmacy is a well-known problem in advanced cancer causing potential drug-drug interactions (DDIs), which, in turn, may limit the therapeutic value of CDK4/6 inhibitors. Therefore, understanding the mechanisms underlying potential DDIs in patients taking CDK4/6 inhibitors may be useful in decision-making processes and represent an important step towards treatment personalization. The present review is aimed at describing the potential DDIs that might occur in breast cancer patients receiving CDK4/6 inhibitors based on direct evidence from the literature and mechanistic considerations tailored on specific class of drugs used in combination.

Introduction

Clinical pharmacology of CDK4/6 inhibitors at a glance

Pharmacodynamics

CDK4/6 inhibitors, namely palbociclib, ribociclib and abemaciclib, belong to a new class of anticancer drugs used for the treatment of patients with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. Studies on the structure-activity relationship suggest that the presence of the 2-amino-pyridine group and the piperazine ring (Fig. 1) are important molecular determinants for ATP-competitive inhibition and CDK4/6 selectivity [1]. Abemaciclib has the highest CDK4/CDK6 selectivity ratio within the class and the unique ability to target CDK9 at clinically relevant concentrations [2]. These properties may account, at least partially, for single-agent activity of abemaciclib in breast cancer patients [3], whereas the other CDK4/6 inhibitors showed comparable efficacy in combination with hormonal therapy [4]. CDK4/6 inhibitors can also modulate the tumor microenvironment leading to immune cell activation and tumor clearance. This mainly occurs trough an increased expression of genes associated with inflammatory T-cell phenotype, a reduction of regulatory T cell activity, and an activation of mechanisms that favor antigen processing for MHC class II presentation [5–7].

Pharmacokinetics

Pharmacokinetics of CDK4/6 inhibitors is depicted schematically in Fig. 2 and parameters are reported in Table 1. Palbociclib is administered orally at 125 mg once daily by a 3 weeks on/1 week off schedule, in combination with an aromatase inhibitor (as initial therapy in postmenopausal women) or fulvestrant (in women who have received prior endocrine therapy) [4]. Food has been reported to reduce pharmacokinetic variability of palbociclib [8,9] as well as the impact of DDIs when concomitant administration of proton-pump inhibitors is required [10]. Drug metabolism occurs by CYP3A and SULT2A1, and the high volume of distribution (V_d) of 2793 L indicates substantial tissue binding [9]. Penetration of palbociclib into the central nervous system may be limited to some extent by efflux transporters (P-gp and BCRP) at the blood-brain barrier level [11,12]. Renal excretion is a minor route of elimination with a mean of 1.8% of unchanged drug found in urine and the elimination half-life ($t_{1/2}$) of palbociclib (about 26 h) is consistent with the once-daily schedule [9].

Ribociclib is used in combination with an aromatase inhibitor, as

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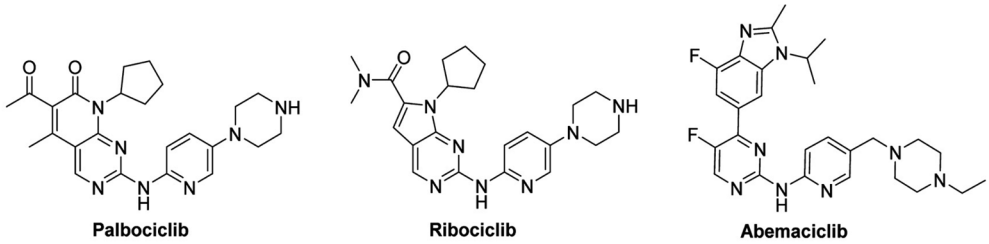

Fig. 1. Chemical structures of CDK4/6 inhibitors [58].

initial therapy for postmenopausal women with HR+ HER2− advanced breast cancer [4]. Overall exposure of a single oral dose of 600 mg in healthy volunteers does not significantly change in fed versus fasted states [13]. Furthermore, there is no impact of gastric pH-altering agents on drug absorption [14]. Ribociclib is rapidly absorbed with a time to maximum plasma concentration (T_{max}) of 1 to 5 h and daily administration is justified by a $t_{1/2}$ of 33 to 42 h (Table 1). Ribociclib undergoes extensive hepatic metabolism mediated by CYP3A4 and the main active metabolite (LEQ803) accounts for approximately 10% of the parent drug [15].

Abemaciclib is administered twice daily at 150 mg in combination with fulvestrant or at 200 mg as monotherapy. Selection of these dose levels was supported by the clinical dose-response relationship for target engagement and the correlation of p-Rb suppression to clinical activity. Drug doses can be scaled up or down depending on clinical evidence of efficacy and/or toxicity [16]. Data from a phase I trial demonstrated that abemaciclib dose adjustments are not required for adult patients of different sex, age, or body weight [16]. The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% and the median T_{max} ranges from 4 to 6 h (Table 1). The AUC values of abemaciclib and its active metabolites increase by 9% when administered with a high-fat meal in healthy subjects. Abemaciclib is extensively metabolized by CYP3A4 with formation of equipotent active metabolites [17]. The V_d is approximately 690 L. Improved central nervous system penetration has been demonstrated for abemaciclib with concentrations of parent drug and active metabolites in cerebrospinal fluid comparable to unbound plasma concentrations [12,18]. Approximately 81% of the dose of abemaciclib is eliminated in feces as metabolites and the elimination $t_{1/2}$ is 18.3 h, which is consistent with the twice-daily schedule used in breast cancer (Table 1).

Table 1
Comparison of key pharmacokinetic characteristics of CDK4/6 inhibitors.

	Palbociclib	Ribociclib	Abemaciclib
Dose (mg)	125 q.d.	600 q.d.	200 b.i.d.
Schedule	3 weeks on/1 week off	3 weeks on/1 week off	Continuous
Metabolism	CYP3A and SULT2A1	CYP3A4	CYP3A4
Active metabolites	No	Yes (LEQ803, CCI284)	Yes
C_{max} (ng/ml)*	52	~1000	298
T_{max} (h)	7	~5	8
$t_{1/2}$ (h)	25.9	32.6	17–38
V_d (l)	2793	1090	690.3
AUC (ng/mlxh)	299#	~20,000∞	5520
CNS penetration	+	NA	+ + +

NA: not available. References [9,15].
* First cycle day 1.
\# $AUC_{0\text{-}10}$.
∞ $AUC_{0\text{-}24}$.

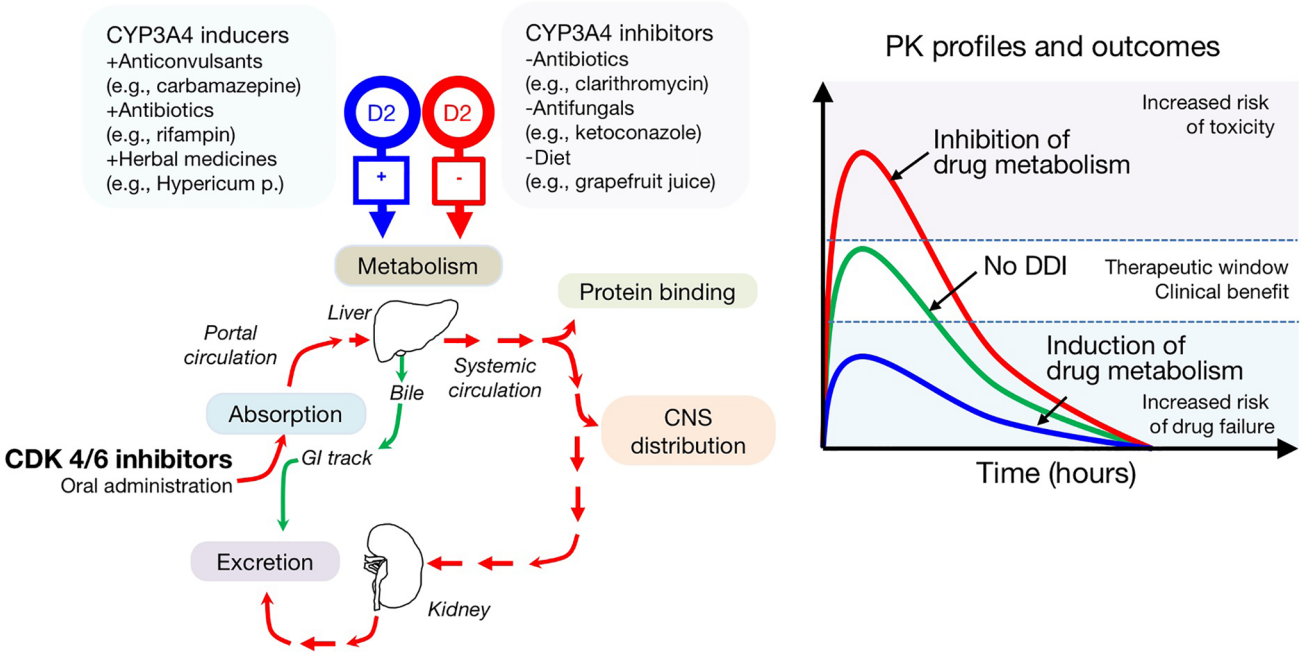

Fig. 2. Pharmacokinetic overview of CDK4/6 inhibitors. Drugs are administered by oral route and, after absorption from the gastrointestinal tract, they can reach the systemic circulation through the portal system. Drugs undergo extensive hepatic metabolism mediated mainly by the CYP3A4 isoform. Tissue distribution is influenced by plasma protein binding and penetration into the central nervous system (CNS) depends on drug lipophilicity. Drug elimination mainly occurs through biliary excretion, whereas renal excretion is negligible. The metabolism of CDK4/6 inhibitors can be altered by concomitantly administered second drugs (D2) with possible clinical consequences.

Table 2
Incidence of adverse drug reactions (ADRs) with CDK4/6 inhibitors.

ADRs (%)	Palbociclib		Ribociclib		Abemaciclib	
	Any grade	(Grade 3/4)	Any grade	(Grade 3/4)	Any grade	(Grade 3/4)
Neutropenia	81	65	74	58	41–46	22–27
Febrile neutropenia	2	1	NR	1.5	< 1	< 1
Anemia	28	5	17–19	2–3	28–29	6–8
Leukopenia	45	27	27–33	13–21	21–28	8–10
Thrombocytopenia	19	2	9	NR	10–16	2–3
Diarrhea	19–26	0–4	29–35	1	81–90	9–20
Nausea	25–35	0–2	51.5	2.4	39–64	1–4.5
Vomiting	14	0–1	29	4	NR	NR
Increased ALT	8	2	15–46	6–10	13–16	4–6
Increased ALT	9	3	13–44	5–7	12–15	2–3
Fatigue	37–39	2	36.5	2	40–65	2–13
QTc prolongation*	NR	1	6.2	NR	NR	1

NR: No evidence was reported.
* In the PALOMA-3 trial, only one patient experienced QT prolongation (SAE of grade 3), which resolved within 2 days. In MONARCH 1, only one patient discontinued the treatment due to QT prolongation. References: [22,23,26,44].

Safety

CDK4/6 inhibitors induce hematological adverse events (Table 2). In particular, neutropenia represents the main dose-limiting toxicity for this class of drugs and it is most frequently observed in patients treated with palbociclib or ribociclib [19]. Neutropenia induced by CDK4/6 inhibitors is dose-dependent, rapidly reversible, usually not associated with febrile neutropenia, and manageable by dose delay or reduction [19]. This appears to be in line with evidence showing bone marrow suppression through cell cycle arrest without apoptosis at clinically relevant concentrations of palbociclib, with resumed proliferation following drug withdrawal [20]. These findings also support the intermittent dosing regimen for palbociclib and ribociclib, which provides time for bone marrow cells to recover during the 1-week treatment-free period. Due to a lower incidence of neutropenia on abemaciclib compared to palbociclib or ribociclib, abemaciclib can be given on a continuous dosing schedule [21].

The incidence of all-grade gastrointestinal (GI) toxicities is higher in patients treated with abemaciclib than in patients given palbociclib or ribociclib, although high-grade (3–4) events are relatively uncommon (Table 2) [22]. GI adverse drug reactions are generally well controlled by standard antiemetic (e.g., metoclopramide, serotonin 5-HT3 antagonists), while the prophylactic administration of loperamide is recommended to prevent diarrhea in patient treated with abemaciclib [23]. Fatigue, alopecia and stomatitis have also been reported among patients treated with this class of drugs [24].

Treatment-related QTc interval prolongation on ribociclib was observed in patients with Rb positive advanced solid tumors or lymphomas [15] (Table 2). Such an effect is generally asymptomatic, reversible upon drug cessation, and depends on the administered dose, occurring in 9% of patients treated with 600 mg/day 3-weeks on/1-week off and in 33% of those receiving higher ribociclib doses [15]. Patients receiving ribociclib therefore undergo electrocardiograms and electrolytes monitoring prior to initiation of treatment and during follow-up. Furthermore, the risk of an additive adverse reaction should be carefully taken into account in ribociclib-treated patients having other conditions associated to QTc interval prolongation [25]. The risk of *Torsade de pointes* (TdP) does not seem to be a class effect since no QTc prolongation events were observed in patients treated with abemaciclib or palbociclib [26]. The mechanism of drug-induced QTc prolongation involves the human ether-a-go-go-related gene (hERG) that encodes the pore-forming subunit of the rapidly activating delayed rectifier potassium channel (IKr), which is important for cardiac repolarization. Dysfunction of hERG causes long QT syndrome and sudden death, which occur in patients with cardiac ischemia [27]. All drugs known to prolong the QT interval were shown to block the hERG channels in cardiac myocytes. However, the chemical structures of these drugs can be very different [28].

Potential DDIs in patients treated with CDK4/6 inhibitors

Pharmacokinetic-based DDIs

Pharmacokinetic interactions occur when two or more drugs are substrates of the same enzymes/transporters involved in their absorption, metabolism, disposition and/or excretion. These types of DDIs can substantially affect the exposure levels of drugs with the consequent potential increase of significant type A (augmented) or F (failure) ADRs [29] (Fig. 2).

CYP3A4-based DDIs

CYP3A4 plays a pivotal role in metabolism of CDK4/6 inhibitors and the low substrate specificity makes it a susceptible target for reversible or irreversible inhibition by a large number of drugs (Fig. 2). The irreversible CYP3A4 inhibition (i.e., inactivation by the formation of metabolic intermediates that bind tightly to the enzyme) more frequently causes DDIs than reversible inhibition, as the inactivated CYP3A4 has to be replaced by newly synthesized protein [30]. For instance, when erythromycin or clarithromycin is co-administered with terfenadine, astemizole, or pimozide, patients may experience TdP [30], whereas older people taking CYP3A4-metabolized statins and clarithromycin or erythromycin were hospitalized more frequently for rhabdomyolysis and acute kidney injury [31].

Patients experiencing neutropenia after treatment with anticancer agents may benefit most from antibiotic, antifungal, and antiviral prophylaxis [32]. However, caution is required in the presence of multiple treatments and the choice of the antimicrobial agent should be carefully evaluated. For instance, co-administration of CDK4/6 inhibitors with strong CYP3A inducers demonstrated to decrease plasma concentrations of the CDK4/6 inhibitor leading to potential drug failure [33]. A paradigmatic example of such a type of interaction has been shown in healthy subjects, where the administration of rifampin was associated to an 85% and 95% decrease in plasma AUC of palbociclib and abemaciclib, respectively [33]. According to this, rifampin decreased the plasma exposure of palbociclib in healthy subjects by 85% [21], suggesting that concomitant use of strong CYP3A inducers and CDK4/6 inhibitors should be avoided in breast cancer patients and a non-interacting alternative considered (Table 3).

The opposite scenario may occur in breast cancer patients treated with strong CYP3A4 inhibitors (Fig. 2), which have been demonstrated to increase the pharmacokinetic exposure of CDK4/6 inhibitors to a

Table 3
Pharmacokinetic-based DDIs between CDK4/6 inhibitors and various drug classes. Red: potential increase of significant type A or F ADRs; yellow: potential increase of moderate type A or F ADRs; green: no increase of type A or F ADRs. Legend: Cat: Category.

Mechanism	Perpetrator drugs	Risk of DDIs			
		Strength	Likelihood	Impact	Cat.
CYP3A inhibition	Clarithromycin, telithromycin	Strong	Intermediate	High	
	Erythromycin	Moderate	Intermediate	Intermediate	
	Azithromycin	Weak	Intermediate	Low	
	Itraconazole, ketoconazole, posaconazole	Strong	Intermediate	High	
	Fluconazole, voriconazole	Moderate	Intermediate	Intermediate	
	Ritonavir	Strong	Very low	High	
	Saquinavir	Moderate	Very low	Intermediate	
	Diltiazem, verapamil	Moderate	Intermediate	Intermediate	
	Fluoxetine, fluvoxamine	Weak	Intermediate	Low	
CYP3A induction	Rifampin	Strong	Low	High	
	Efavirenz	Moderate	Very low	Intermediate	
P-gp inhibition	Isavuconazole, ketoconazole, itraconazole	Strong	Intermediate	High	
P-gp induction	Rifampin	Strong	Intermediate	High	

Classification of DDIs is based on The Flockhart Table™. Strong inhibition: > 5-fold increase in the plasma AUC values or > 80% decrease in clearance of a victim drug; moderate inhibition: > 2-fold increase in the plasma AUC values or 50–80% decrease in clearance of a victim drug; weak inhibition: > 1.25-fold but < 2-fold increase in the plasma AUC values or 20–50% decrease in clearance of a victim drug [59]. Green box: no change; Yellow box: reduce the dose of CDK4/6 inhibitor or consider alternative secondary drugs; Red box: avoid combination and consider alternative secondary drugs.

clinically meaningful extent, potentially leading to increased toxicity [21]. For example, co-administration of clarithromycin has been reported to increase abemaciclib AUC by 237% and C_{max} by 30%, respectively, and those of the total active metabolites by 119% and 7%, respectively [33]. As a consequence, clarithromycin and abemaciclib combination should be avoided or, alternatively, abemaciclib dose should be reduced from 200 or 150 mg to 100 mg twice daily [17]. Accordingly, daily dose of palbociclib needs to be reduced from 125 to 75 mg and that of ribociclib from 600 to 400 mg, in the presence of strong CYP3A4 inhibitors [21].

The time-dependent offset of CYP3A4 inhibition may account for some serious adverse reactions associated with discontinuation of irreversible inhibitors and immediate initiation of a second drug treatment [30]. Therefore, it is important to apply an appropriate washout period before giving the second potentially interacting drug. In case of discontinuation, the CDK4/6 dose intensity should be returned to *status quo ante* after 3–5 half-lives of the perpetrator drug only [21]. Another feasible approach to mitigate the consequences of DDIs, while maintaining the class effect may consist in using other members of the same group of drugs having little or no effect on CYP3A4 activity. For example, azithromycin has a negligible effect on CYP3A4 (i.e., it does not inhibit CYP3A4 or increase blood concentrations of CYP3A4-metabolized statins) and could be given to patients receiving CDK4/6 inhibitors in place of clarithromycin [31] (Table 3). Finally, it should be noted that breast cancer patients treated with CDK4/6 inhibitors have a very low risk to develop febrile neutropenia and, anti-pseudomonas β-lactam agents, i.e., drugs proven not interacting with CYP3A4-metabolized substrates [34], are the first choice treatment for high-risk patients who require hospitalization for intravenous antibiotic therapy [32], in those uncommon cases of febrile neutropenia and risk of septic shock.

Cancer patients who have persistent fever after a broad-spectrum antibacterial regimen may also benefit from empirical antifungal treatments. However, selection of a specific antifungal agent needs to be carefully evaluated by taking into account that DDIs involving antifungals are common during multiple treatments [32,35]. For example, ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold with potential toxicity; this combination should be therefore avoided and non-interacting alternatives considered in patients receiving CDK4/6 inhibitors [17]. A possible alternative is represented by echinocandins, which display a lower potential for DDIs [35]. Indeed, they do not promote a marked inhibition of P450 activities *in vitro* and the blood/plasma concentrations of concomitant CYP3A4-metabolized drugs were not markedly affected by co-administration of echinocandins *in vivo* [36]. This drug class could therefore represent a valid alternative to azole derivatives in patients administered with CDK4/6 inhibitors.

Several lines of evidence indicate that immunosuppressed transplant recipients and HIV-infected patients have a diminished incidence of breast cancer relative to other malignancies [37]. Because of this, patients having both HIV and breast cancer are very rare [37], suggesting that co-administration of anti-HIV treatments and CDK4/6 inhibitors is uncommon in the real-life setting. However, the aggressiveness of breast cancer in the rare cases of HIV-positive women justifies every effort to preserve the dose intensity of treatment [38]. Avoiding unexpected adverse drug reactions is important, especially taking into account the current near-normal life expectancy for HIV-positive patients. Potential concerns on the concomitant use of CDK4/6 inhibitors and antiretroviral drugs are discussed in the “Complex DDIs” section below.

P-gp/BCRP-based DDIs

P-glycoprotein (P-gp) and BCRP (Breast Cancer Resistance Protein) belong to the superfamily of ATP-binding cassette (ABC) transporters, which play a pivotal role in absorption, distribution and elimination of a large number of drugs [11,39]. P-gp- and BCRP-based DDIs may therefore have important clinical implications, particularly in terms of intestinal absorption and distribution of drugs across the blood–brain barrier (BBB) [40]. For example, in healthy volunteers, rifampin treatment (600 mg/d for 10 days) increased intestinal P-gp content by 3.5-fold and markedly reduced digoxin plasma concentrations after oral administration [41]. Although no evidence has been provided in breast cancer patients, CDK4/6 are substrates of P-gp [12] and rifampin-mediated intestinal P-gp induction is expected to decrease CDK4/6 bioavailability after oral administration. However, the consequences of P-gp induction by ripampicin on abemaciclib pharmacokinetics could be more difficult to predict, since abemaciclib has been demonstrated to inhibit P-gp and BCRP activities at clinically reachable concentrations [39].

Increased bioavailability of CDK4/6 inhibitors can be expected in the presence of antifungal azoles, namely isavuconazole, ketoconazole, and itraconazole, as they are strong P-gp inhibitors [35]; in this case, dose reduction of CDK4/6 inhibitors may be appropriate as well as the use of non-interacting antifungal agents (Table 3).

In the blood-brain barrier, the presence of efflux transporters such as P-gp and BCRP have been reported to limit the distribution into the

central nervous system (CNS) of palbociclib compared to abemaciclib [3,4]. Abemaciclib drug levels in the brain can be reached at lower doses compared to palbociclib most probably because of the higher lipophilicity of abemaciclib (cLogP value of 5.5 and 2.7, respectively) [2] as well as through the P-gp/ BCRP inhibitory effect of abemaciclib [39]. Antifungal azole can competitively interact with P-gp at the blood-brain barrier level [42] in such a way to favor the CNS penetration of P-gp substrates, including CDK4/6 inhibitors.

Pharmacodynamic-based DDIs

Pharmacodynamic interactions are usually characterized by overlapping on-target and/or off-target effects by two or more drugs concomitantly administered to a patient. They can involve either an additive, synergistic, or antagonistic interaction that may favor or harm the patient. Often the interaction is indirect and involves interference with physiological mechanisms; indeed, if two drugs sharing the same toxicological effect are given together, the resulting effect can be additive [29].

A paradigmatic example of pharmacodynamic-based DDIs potentially occurring in patients receiving CDK4/6 inhibitors derives from the concomitant administration of ribociclib and heart rate-corrected QT (QTc)-prolonging drugs. Although QT prolongation is usually considered necessary but not sufficient to induce TdP, an increased risk for TdP may occur whenever QTc exceeds 500 ms or a drug rapidly increases QTc by > 60–70 ms [43]. In the MONALEESA-3 trial, QT interval prolongation (any grade) was reported in 6.2% of patients receiving ribociclib plus fulvestrant, with 0.6% of them discontinuing study treatment [44]. TdP and fatal ventricular arrhythmia, although rare, might therefore occur in patients treated with ribociclib as a consequence of additive effect by QTc-prolonging drugs (Table 4) and/or other medical conditions (Table 5).

Drugs causing QT interval prolongation

Anticancer drugs. Preclinical and clinical investigation suggest that tamoxifen may cause QT interval prolongation in humans by blocking the rectifier potassium current [37,38]. Furthermore, 5-fluorouracil and its pro-drug capecitabine [39,40] as well as anthracyclines [45] have been reported to induce QT prolongation with TdP and ventricular tachycardia in women with early breast cancer. A possible strategy to avoid potential additive effects in patients pretreated with tamoxifen and/or chemotherapy, is to initiate ribociclib treatment after five half-lives of the previously discontinued drug. While such an approach appears to be unfeasible for tamoxifen due to its long elimination half-life ($t_{1/2}$, 7 days), it could be feasible for epirubicin and 5-fluorouracil ($t_{1/2}$ of ~30 h and 10 min, respectively). Intensifying ECG monitoring during follow-up or selecting alternative CDK4/6 inhibitors (i.e., abemaciclib or palbociclib) having little or no effects on QT interval [26] may also be valid alternatives (Table 4).

Antiemetic drugs. Chemotherapy-induced nausea and vomiting is one of the most common adverse effects of CDK4/6 inhibitors and 5-HT3-receptor antagonists are frequently used to treat this adverse reaction. Unfortunately, QT prolongation is a class effect of the 5-HT3-receptor antagonists and caution is required when administering these drugs in patients using ribociclib (Table 4). However, while conflicting evidence on a possible risk of TdP has been provided for granisetron and tropisetron, no significant change in QTc interval was observed for palonosetron, a second-generation drug with higher affinity for 5-HT3 receptors and longer half-life than first-generation drugs [46]. Clinical trials carried out using NK-1 receptor antagonists as single agents (e.g., aprepitant and fosaprepitant) or in combination schedules (i.e., netupitant plus palonosetron), suggest that this class of drugs is not associated with a significant QTc interval prolongation. Therefore, adoption of antiemetics with low risk of QT prolongation (e.g., palonosetron or NK-1 receptor antagonists) together with ECG monitoring could be used as an alternative antiemetic strategy to reduce the risk of arrhythmic events in breast cancer patients receiving ribociclib [46].

Table 4
Predicted risk of torsade de pointes of various drug classes often used in breast cancer patients during or before ribociclib.

Drug categories	Risk of torsade de pointes		
	Likelihood	Impact	Cat.
Cancer			
Tamoxifen, epirubicin, 5-fluorouracil	High	Intermediate	
Gastrointestinal disorders			
Ondansetron, dolasetron, domperidone, chlorpromazine, metoclopramide	High	High	
Granisetron, tropisetron	High	Intermediate	
Palonosetron, aprepitant, fosaprepitant	High	Low	
Loperamide	High	Low	
Esomeprazole	Intermediate	Low	
Pain			
Methadone, oxycodone	High	High	
Tramadol, ketorolac	High	Intermediate	
Microbial infections			
Erythromycin, clarithromycin	Intermediate	High	
Azithromycin	Intermediate	Intermediate	
Ciprofloxacin, levofloxacin, moxifloxacin	Intermediate	High	
Norfloxacin, gemifloxacin, ofloxacin	Intermediate	Intermediate	
Fluconazole	Intermediate	High	
Voriconazole	Intermediate	Low	
Efavirenz	Intermediate	Intermediate	
Atazanavir	Low	Intermediate	
Anesthesia			
Propofol, sevoflurane	Intermediate	High	
Psychiatric disorders			
Citalopram, escitalopram	Intermediate	High	
Venlafaxine	Intermediate	Intermediate	
Paroxetine, fluoxetine, sertraline	Intermediate	Low	
Chlorpromazine	High	High	
Thioridazine	Low	High	

Risk of Torsade de pointes is based on the likelihood that a DDIs can actually occur in breast cancer patients receiving ribociclib, and on the QT prolongation potential of perpetrator drugs [60]. Green box: no change; Yellow box: initiate ribociclib dose after five half-lives of secondary drug discontinuation or, intensify ECG and clinical monitoring or, consider alternative secondary drugs or less arrhythmogenic CDK4/6 inhibitors; Red box: avoid combination and consider alternative secondary drugs or less arrhythmogenic CDK4/6 inhibitors. GERD: gastroesophageal reflux disease. NCI classification of QT interval prolongation (QTc, ms): grade 1 (450–480); grade 2 (481–500); grade 3 (> 501 ms on at least two separate electrocardiograms); grade 4 (> 501 ms or a change of > 60 ms from baseline); torsades de pointes (polymorphic ventricular tachycardia, or signs or symptoms of severe arrhythmia) [26].

Analgesic drugs. Opioid analgesics are a cornerstone of severe pain treatment including cancer pain [47]. Several drugs in this class endowed with a bi-phenyl ring structure (e.g., propoxyphene and methadone) have an important QT prolongation potential [48,49], while those which differ structurally (e.g., buprenorphine) has a less potent QT prolonging effect. Furthermore, morphine does not significantly change the QTc interval [48] and should be selected in patients treated with ribociclib. Important to note, buprenorphine, fentanyl and alfentanil could be used as a valid alternative to morphine in opioid rotation in ribociclib-treated patients since no QTc prolongation-related issues were reported for these drugs [48]. No QTc effects were observed at supratherapeutic doses of the opioid/nonopioid analgesics tramadol [50] and tapentadol [51].

Psychiatric drugs. Depression is common in cancer patients and, due to the lack of efficacy data from head-to-head clinical comparison, the safety profile is often used to guide the antidepressant selection [52]. In case of breast cancer patients treated with ribociclib, clinicians should

Table 5
Genetic and epigenetic factors associated with increased susceptibility of breast cancer patients to develop clinically relevant torsades de pointes when exposed to ribociclib.

Type	Conditions	Likelihood
Comorbidities	Hypothyroidism, hypothermia, extreme bradycardia, cardiac disorders, kidney failure, liver dysfunction, poorly controlled diabetes	High
Electrolyte abnormalities	Hypokalemia, hypomagnesemia, and hypocalcemia	
Disorders associated with cancer therapy	Nausea/vomiting and dehydration	High
Gender	Risk increased in females (estrogen-mediated reduced repolarization reserve)	Very high
Genetic variants		Very low

TdP: Torsade de pointes. References: [24,40,56,57].

pay attention to antidepressants with QT prolongation potential, particularly citalopram and escitalopram (Table 4).

Antimicrobial agents. Several antimicrobial agents have the potential to induce clinically relevant QT prolongation effects (Table 4). Macrolides can affect repolarization in the His-Purkinje tissue and the M cells in the ventricular myocardium and such an effect appears to be related to the rate of drug infusion [53]. Since azithromycin has been proved to be the least likely macrolide to cause cardiac arrhythmias (Table 4) [53], this drug should be used as a first choice in those ribociclib-treated patients who required therapy with this class of drugs. Fluoroquinolones have also been associated to QT interval prolongation with various levels of evidence (Table 4). Particularly, fluconazole may cause prolongation of QTc syndrome via a double mechanism consisting of the direct inhibition of rectifier potassium current, the main repolarizing current and disruption of hERG protein trafficking [54]. Combination of ribociclib with antifungal azoles should be avoided and alternative drugs should be used. Whenever azole treatment is strictly required, voriconazole should be preferred and clinical/ECG monitoring carried out in patients receiving ribociclib (Table 4).

Complex DDIs

Several lines of evidence indicate that a great number of DDIs may often occur by two or more mechanisms acting in concert [29], which makes the prediction of DDIs in patients treated with CDK4/6 inhibitors more complex. For example, combination of fluoroquinolones and azoles can be used as prophylaxis or treatment of infections in neutropenic cancer patients [55]. Unfortunately, many of these drugs have QTc prolonging potential [55] and the use of this combination should be avoided in at-risk patients for long QT syndrome, including those receiving ribociclib. Beside representing an additional risk factor for QT prolongation *per se*, the torsadogenic potential of ribociclib may be further increased as a consequence of azole-mediated CYP3A4 inhibition. The ability of antifungal azoles to competitively interact with P-gp substrates [42] may represent another mechanism that could alter the pharmacokinetics of CDK4/6 inhibitors.

Multiple mechanisms may also characterize potential clinical DDIs between rifampicin and CDK4/6 inhibitors. Rifampin can affect other physiological processes beside CYP3A4, including P-gp [41] and UGT induction [56], that need to be considered as likely perpetrator mechanisms in patients receiving CDK4/6 inhibitors.

Drug metabolism may also increase the complexity of data interpretation. For instance, the HIV protease inhibitor nelfinavir is primarily metabolized by CYP2C19; this drug is capable of increasing simvastatin plasma levels and the risk of rhabdomyolysis through its metabolite, which strongly inhibits CYP3A4 [57].

Finally, the planned combination of antiretrovirals belonging to the same drug class makes the clinical consequences of their interaction with CDK4/6 inhibitors unpredictable. For instance, it has been recognized that saquinavir has the lowest inhibition potency on CYP3A4 within the class and is expected to induce only modest changes in the pharmacokinetics of CYP3A4 substrates. However, HIV treatment may include ritonavir-boosted schedules to achieve higher sustained levels of the second protease inhibitor and ritonavir/saquinavir has been shown to strongly increase the exposure to simvastatin acid [57].

Conclusions and future perspectives

CDK4/6 inhibitors are innovative targeted drugs that have recently enriched the treatment landscape of breast cancer. Polypharmacy is very common in cancer patients and DDIs can affect the pharmacokinetics and/or pharmacodynamics of these drugs thus adding complexity to the optimal management of subjects taking CDK4/6 inhibitors, by exposing patients to under-treatment or severe adverse drug reactions. As regards the latter, it is important to note that although drugs belonging to this class have similar clinical efficacy, their toxicity profile is quite different. In particular, hematological toxicity and diarrhea are respectively less and more frequent in patients taking abemaciclib than palbociclib or ribociclib, whereas incidence of liver function abnormalities is higher for ribociclib than palbociclib or abemaciclib. Furthermore, the risk of an additive adverse reaction should be taken into account particularly in ribociclib-treated patients having other conditions predicted to prolong the QTc interval. Understanding the mechanisms of DDI, together with the integrated knowledge of patient/drug-specific characteristics, may therefore represent the basis for optimal therapeutic decision-making in patients receiving CDK4/6 inhibitors. Owing to the complexity of treatment personalization, a multidisciplinary approach involving clinical pharmacologists and oncologists is warranted for the optimal treatment of the patient.

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