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The Pharmacological Profile of Cyclin-dependent Kinase (CDK) 4/6 Inhibitors: Clinical Management of Toxicity and Drug Interactions Related to CDK 4/6 Inhibitor-based Treatment in Advanced/Metastatic Breast Cancer

Review Article

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Abstract: The emergence of cyclin-dependent kinase (CDK) 4 and 6 inhibitors has brought a new approach in the treatment of advanced hormone receptor (HR) positive breast cancer and human epidermal growth factor (HER) 2 negative breast cancer. To date, three CDK 4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, are approved by the Food and Drug Administration (FDA); the first two agents are approved by the European Medicines Agency (EMA) as well. The family of CDKs consists of key regulatory enzymes that play a significant role in cell cycle progression. The aim of this review is to give an overview of the mechanism of action and the efficacy of CDK4/6 inhibitors and to highlight the most serious adverse events and the drug interactions related to these agents.

Keywords: *Breast cancer • CDK4/6 inhibitors • toxicity • drug interactions • clinical management*

1. Background

One of the most important hallmarks of cancer is the ability of cancer cells to sustain aberrant proliferative signaling, resulting in immortality [1]. In normal tissues, a number of proteins have the significant role of tightly regulating the process of cell proliferation [2]. In this way, under the strict regulation of the cell cycle machinery, cells divide without aberrations [3]. Cyclin D-dependent kinases, in particular CDK 4 and 6, play a critical role as regulators of cell cycle by controlling the transition from the G1 to the S phase [4]. CDK1 regulates the transition from the G2 to the M phase, while CDK2 regulates the transition through the S phase [5]. A number of preclinical trials in breast cancer have shown that abnormal tumor cell proliferation is related to the hyperactivity of the cyclin D-CDK4/6 axis, making the inhibition of this pathway an interesting target for the treatment approach of advanced/metastatic estrogen receptor positive (ER(+)) and human epidermal growth factor receptor 2 negative (HER2(−)) breast cancer in combination with endocrine therapy [6]. Additionally, the role of the tumor suppressor retinoblastoma protein (Rb) for the transition from the G1 to the S phase of cell cycle is well known [7],[8]. Retinoblastoma is a gene product that promotes this transition after being hyperphosphorylated by the complex cyclin D-CDK 4 and 6 [9]. Several alterations of the CDK4/6-Rb pathway can result in overactivation of CDK4/6 that can lead to attenuation of senescence and promotion of uncontrolled cell division [5],[7],[10]. In this short review we will focus on the mechanism of action of CDK4/6 inhibitors and the management of the most common adverse events and drug interactions related to the treatment of breast cancer with these new agents.

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2. Mechanism of action of CDK4/6 inhibitors: The cyclin D-CDK4/6-INK4 (inhibitor of CDK4)-Rb pathway

To date, the subtypes of breast cancer in which CDK4/6 inhibitors have shown clinical benefit are hormone receptor positive (HR+) and HER2− [3],[11]–[14]. In HR+ breast cancer there is high expression of ER and/or progesterone receptor (PR) and dependence from the ER signaling pathway for the growth and survival of cancer cells [15]. While estrogen drives the ER signaling pathway to facilitate a number of cellular functions, such as the cell proliferation and procedures of apoptosis and angiogenesis, HR+ breast cancers use these regulating functions in favor of tumor growth, development, and progression [15]. This observation led to the introduction of the following agents in the therapeutic field of HR+ breast cancer: the aromatase inhibitors such as anastrozole, letrozole, and examestane, selective ER modulators such as tamoxifen, and selective ER down regulators such as fulvestrant. CDK4/6 inhibitors in combination with endocrine therapy have shown improved progression-free survival (PFS) in HR+/HER2− advanced/metastatic breast cancer [13].

Since the promotion of tumor growth is driven by the action of ER pathway in HR+ breast cancer, its inhibition would prevent the cancer's development [15]. Indeed, the efficacy of endocrine therapy in this subtype of breast cancer is undeniable. In some patients, though, this efficacy can be limited due to acquired or preexisting resistance [15]. The fact that both ER signaling pathway and alternative survival pathways use the cyclin D-CDK4/6-INK4-Rb pathway led to the addition of CDK4/6 inhibitors to endocrine therapy in order to prevent the tumor growth [7], [11]–[14], [16], [17].

The development and proliferation of normal cells undergo strict regulation by external growth signals and the cell cycle machinery [2]. All phases of cell cycle, G1, S, G2, and M phase, are controlled by a number of "checkpoints" that prevent any damage or defect before entering the M phase, in order to protect daughter cells from carrying damaged DNA [18]. Breast cancer cells, like all tumor cells, are characterized by dysregulation of these "checkpoints," resulting in uncontrolled proliferation and survival of cancer cells [6].

The passage from the G1 to the S phase of cell cycle is very crucial, because it promotes the cell to enter the M phase irreversibly [19]. The cyclin D-CDK4/6-INK4-Rb pathway plays a key role in the control of transition from the G1 to the S phase [20]. During phase G, the inactive complex between Rb and E2F transcription factor regulates the prevention of gene's expressions required for the cell to enter the S phase and proceed to cell division [7]. Concomitantly, the ER pathway, a mitogenic signaling pathway, regulates the expression of cyclin D through *CCND1* gene, allowing the formation of cyclin D-CDK 4 or 6 complex [21]. CDK 4 and 6 are serine-threonine kinases with structural, biochemical, and biological similarities [20]. The complex cyclin D-CDK4/6 is stabilized by proteins, such as p21. The active holoenzyme monophosphorylates Rb protein that causes derepression of the transcription factors E2F family [10]. E2F is then active and enables the expression of another, very important factor for the S phase, cyclin E [10]. Binding of cyclin E to CDK2 causes its activation by which Rb protein becomes hyperphosphorylated, leading to further liberation of E2F transcription factors [22], [23]. This sequence of functions results in promotion of transition from the G1 to the S phase through the expression of multiple genes [7], [17], [20].

In ER+ breast cancer there is disruption of the abovementioned axis leading to promotion of tumor growth through hyperactivity of this pathway [6]. The mode of action of the three CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, consists of blockade of Rb phosphorylation, leading to inactive E2F transcription factors and induction of cancer cell arrest [16], [17], [23]–[25]. Indeed, the phenotype of cancer cells after the influence of CDK4/6 inhibitors resembles the cellular senescence [16]. In particular, all three CDK4/6 inhibitors are highly selective reversible inhibitors of CDK 4 and 6. Their efficacy has been shown in preclinical and clinical level in ER+/HER2− advanced/metastatic breast cancer, in combination with hormone therapy, or as a single agent in the case of abemaciclib [11], [13], [26].

In particular, the data of the clinical trials concerning all three CDK 4/6 inhibitors are as follows:

Palbociclib: This CDK 4/6 inhibitor was studied in the PALOMA trials. The first-in-human phase I study demonstrated a favorable safety profile of the agent with neutropenia being the main dose-limiting toxicity, but with a very low risk of febrile neutropenia, compared to cytotoxic chemotherapy [27]. The initial dose of 125 mg daily (3 weeks on/1week off) was tested as a single agent in metastatic breast cancer patients with Rb expression [28]. PALOMA 1 was a phase II trial, where palbociclib+letrozole was administered as first-line therapy in advanced ER(+)/HER2(−) breast cancer and showed a 10-month improvement in PFS (20.2 versus 10.2 months) [29]. These impressive results were confirmed by PALOMA 2, a phase III trial,

with median PFS being 24.8 and 14.5 months for the palbociclib and the placebo group, respectively. Also its final analysis demonstrated that in a follow-up of almost 38 months there was a significant delay in the use of chemotherapy after palbociclib was stopped (40.4 and 29.9 months for the palbociclib and the placebo arm, respectively), while quality of patients' life was maintained [30]. Also, in PALOMA 3 palbociclib was studied in endocrine therapy-resistant metastatic breast cancer in combination with fulvestrant as second-line therapy with median PFS 9.5 and 4.6 months for the palbociclib and the placebo group, respectively [31] [32]. The final analysis in PALOMA 3 showed improvement in OS (34.9 and 28 months for the palbociclib and the placebo group, respectively) [28].

Ribociclib: The data concerning this agent are based on the findings of MONALEESA trials. Results from MONALEESA 2, a phase III study, demonstrated median PFS of 25.3 and 16.0 months for ribociclib and the placebo group, respectively, as first-line treatment of advanced ER(+)/HER2(−) breast cancer in postmenopausal women [33] [34]. A phase III study in pre-/perimenopausal women, MONALEESA 7, showed the efficacy of ribociclib+tamoxifen/NSAI+goserelin as initial treatment of advanced ER(+)/HER2(−) breast cancer. Median PFS was 23.8 and 13.0 months for the ribociclib and the placebo group, respectively [35]. Also, MONALEESA 3, a phase III clinical trial, evaluated the efficacy of ribociclib+fulvestrant in patients with advanced ER(+)/HER2(−) breast cancer after progression on endocrine therapy. There was a significant improvement in median PFS: 20.5 and 12.8 months for the ribociclib and the placebo group, respectively [36]. It should be noted that for MONALEESA 7 we also have the results for OS, with the estimated OS at 42 months being 70.2% and 46.0% for the ribociclib and the placebo group, respectively (p = 0.000973 by log-rank test) [37].

Abemaciclib: Clinical trials that concern this agent are MONARCH 1, 2, and 3. MONARCH 1 was a phase II single-arm study in which abemaciclib was administered as monotherapy in advanced ER(+) breast cancer patients who had previously progressed on endocrine therapy. Overall response rate (ORR) was 19.7% and clinical benefit rate (CBR) was 42.4% after administration of the drug in a heavily pretreated group of patients. It should be noted that the median time to response was 3.7 months, median PFS was 6 months, and OS was 17.7 months [38]. MONARCH 2, a phase III study, was designed as second-line therapy with abemaciclib+fulvestrant administered after progression on endocrine therapy for advanced ER(+) breast cancer. The median PFS in the study was 16.4 and 9.3 months for the abemaciclib and the placebo group, respectively, ORR was 48% and 21% for the abemaciclib and the placebo group, respectively, and CBR was 72% for the abemaciclib arm and 56% for the placebo group [39]. Finally, abemaciclib was administered in combination with NSAI (1 mg anastrazole or 2.5 mg letrozole) in MONARCH 3, a randomized, phase III, double-blind, placebo-controlled study as first-line treatment of advanced ER(+) breast cancer. Results are as follows: Median PFS was 28.18 and 14.76 months for the abemaciclib and the placebo group, respectively, ORR was 61.0% in the abemaciclib arm and 45.5% in the placebo arm (measurable disease, p = 0.003), and the median duration of response was 27.39 months in the abemaciclib arm compared to 17.46 months in the placebo arm [40]. Data concerning influence on quality of patients' life for MONARCH 3 are also published, demonstrating an acceptable safety profile and consistency with previous reports [41].

Table 1 summarizes all data concerning clinical trials for palbociclib, ribociclib, and abemaciclib.

The first CDK4/6 inhibitor designed was palbociclib. Its enzymatic IC50 for CDK 4 and 6 is approximately 11 and 15 nM, respectively. In the case of ribociclib the IC50s are 10 and 40 nM, respectively, for CDK 4 and 6, while the most potent CDK4/6 inhibitor seems to be abemaciclib with IC50s 2 and 10 nM for CDK 4 and 6, respectively [12]. All CDK4/6 inhibitors are orally bioavailable agents and demonstrate their action by binding to the ATP-binding pocket within kinases. This binding results in blocking of Rb's phosphorylation mediated by CDK4/6, which in turn causes the cell cycle arrest at the G1–S checkpoint, because E2F remains inactive as a complex with Rb [7], [17]. These observations were demonstrated by inhibition of cancer cell proliferation in Rb(+) cell lines and dose-dependent inhibition of tumor growth in Rb(+) xenograft tumor models [13].

3. Dosing schedule and pharmacokinetics of CDK4/6 inhibitors

CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, are small molecules that underwent strict evaluation after their design in order to prove their efficacy in breast cancer [11], [13]. The trial programs were PALOMA for palbociclib [31], [32], [42]–[45], MONALEESA for ribociclib [33]–[36], [46], and MONARCH for abemaciclib [38], [41], [47], while a number of trials are in progress as there is the suggestion that CDK4/6 inhibitors could offer clinical benefit in other breast cancer subtypes as well [12] [11].

Table 1: Clinical trials of cdk4/6 inhibitors in advanced and metastatic breast cancer.

Design	Patient population	n	Setting	Treatment arms	Median PFS (months)	ORR (%)	CBR (%)	OS
Phase II open-label	Postmenopausal, HR+*/HER2−, ABC	165	1st line	Palbociclib+letrozole versus letrozole alone	20.2 versus 10.2	55 versus 39	81 versus 58	-
Phase III placebo control	Postmenopausal, HR+/HER2−, ABC	666	1st line	Palbociclib+letrozole versus letrozole alone	24.8 versus 14.5	55 versus 44	85 versus 70	-
Phase III placebo control	Pre-, peri-, postmenopausal, HR+/HER2−, ABC	521	2nd line or later	Palbociclib+fulvestrant versus fulvestrant alone	9.5 versus 4.6	25 versus 11	67 versus 40	34.9 versus 28.0 months
Phase III placebo control	Postmenopausal, HR+/HER2−, ABC	668	1st line	Ribociclib+letrozole versus letrozole alone	25.3 versus 16	53 versus 37	80 versus 73	
Phase III placebo control	Postmenopausal, HR+/HER2−, ABC	725	1st line or 2nd	Ribociclib+fulvestrant versus fulvestrant alone	20.5 versus 12.8	40.9 versus 28.7	-	-
Phase III placebo control	Pre-, perimenopausal HR+/HER2−, ABC	672	1st line	Ribociclib+letrozole+goserelin versus letrozole+goserelin alone	23.8 versus 13.0	51 versus 36		70.2% versus 46.0% at 42 months
Phase II	HR+/HER2−, ABC	132	3rd line or later	Abemaciclib 200 mg/12 h continuously	6	20	42.4	17.7 months
Phase III placebo control	Pre-, peri-, postmenopausal, HR+/HER2−, ABC	669	Progress during neoadjuvant/adjuvant ET < 12 months from end of adjuvant ET or during first-line ET for mBC	Abemaciclib 150 mg/12 h continuously+fulvestrant versus fulvestrant alone	16.4 versus 9.3	48 versus 21	72 versus 56	-
Phase III placebo control	Postmenopausal, HR+/HER2−, ABC	493	1st line	Abemaciclib 150 mg/12 h continuously+anastrozol or letrozole versus anastrozol or letrozole alone	28.18 versus 14.76	61 versus 45.5	78 versus 71.5	-

*Hormone receptor-positive
†Human epidermal growth factor receptor 2
†+Advanced breast cancer

Palbociclib was approved by Food and Drug Administration (FDA) in February 2015, ribociclib was approved in March 2017, and abemaciclib in October 2015 received FDA breakthrough therapy designation. The first two agents, palbociclib and ribociclib, are approved by European Medicines Agency (EMA) as well [14]. It should be taken into account that there are differences between the three agents as far as drug administration is concerned. The dosing schedule for the three agents is as follows: The recommended initial dose of palbociclib is 125 mg daily for 3 weeks on, 1 week off, constituting a 28-day cycle [45], of ribociclib is 600 mg daily for 3 weeks on, 1 week off, constituting a 28-day cycle [46], and of abemaciclib is 150 mg twice daily continuously throughout the cycle when given as monotherapy and in combination with endocrine therapy [47]. While ribociclib and abemaciclib can be taken orally with or without food, in the case of palbociclib it was found that the fasted state caused decreased absorption and drug exposure, and it is recommended that the drug should be administered with food [45]–[47].

The three drugs differ in Tmax (time to maximum concentration). The agent with the slower absorption is palbociclib, with Tmax between 6 and 12 hours [45], while ribociclib is rapidly absorbed, with Tmax between 1 and 5 hours [46], and abemaciclib's Tmax is between 4 and 6 hours [47]. The mean half-life (T1/2) for the CDK4/6 inhibitors is approximately 26 hours for palbociclib [45], 33 hours for ribociclib [46], and 17–38 hours for abemaciclib [47]. Steady-state levels of drugs can be reached within 8 days, in the case of palbociclib and ribociclib, while more days are required for abemaciclib to reach steady-state levels due to the shorter half-life of the drug [13].

If there is any need of modification of the dosing schedule, recommendations are as follows: For palbociclib the recommended initial dose is 125 mg daily (3 weeks on/1 week off), with the first dose reduction 100 mg daily and the second 75 mg daily. For ribociclib the initial dose is 600 mg daily (3 weeks on/1 week

off) with the first dose reduction 400 mg daily and the final reduction 200 mg daily. Finally, the recommended initial dose for abemaciclib is 150 mg every 12 hours as monotherapy and in combination with endocrine therapy. The first dose reduction, if required, is 100 mg twice daily and the second and final dose reduction is 50 mg twice daily. Following the second reductions mentioned above for the three agents, no further reduction is recommended and the drug should be permanently discontinued if further unacceptable toxicity occurs [3], [14], [45]–[47].

4. Interactions of CDK4/6 inhibitors with other drugs

In vitro and in vivo studies have shown that all CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, undergo primary hepatic metabolism by CYP3A4 and SULT2A1 (sulfotransferase) in humans. Additionally, it has been shown that CDK4/6 inhibitors are weak, time-dependent inhibitors of CYP3A [3], [14]. The observation above led to specific recommendations regarding the co-administration of CDK4/6 inhibitors with CYP3A4 inhibitors or inducers.

4.1. Concomitant use of CYP3A4 inhibitors

The concomitant use of CDK4/6 inhibitors with CYP3A4 inhibitors should be avoided, because of increased plasma levels of CDK4/6 inhibitors and possible toxicity [3], [14]. If the co-administration of a strong CYP3A4 inhibitor cannot be avoided, we should modify the dose of CDK4/6 inhibitor as follows: Dose adjustment of palbociclib to 75 mg once daily, of ribociclib to 400 mg once daily, and of abemaciclib to 50 mg twice daily. After the discontinuation of the strong CYP3A4 inhibitor we could increase the dose of CDK4/6 inhibitor to the dose used prior to the co-administration (after 3–5 half lives of the CYP3A4 inhibitor) [45]–[47]. The list of strong CYP3A4 inhibitors includes but is not limited to the following agents and substances: Itraconazole, ketoconazole, clarithromycin, erythromycin, telithromycin, voriconazole, posaconazole, indinavir, lopinavir, ritonavir, nelfinavir, nafazodone, verapamil, and grapefruit/grapefruit juice. In case of co-administration of a moderate/weak CYP3A4 inhibitor there is no need of dose adjustment of CDK4/6 inhibitor but close monitoring for possible toxicity is required [3], [14], [45]–[47].

4.2. Concomitant use of CYP3A4 inducers

It has been shown that the co-administration of strong CYP3A4 inducers with CDK4/6 inhibitors leads to reduced levels of CDK4/6 inhibitors in plasma and consequently to reduced efficacy of these agents. The observation above indicates that we should avoid concomitant administration of both, CYP3A4 inducers and CDK4/6 inhibitors. CYP3A4 inducers include but are not limited to: Rifampicin, carbamazepine, phenytoin, enzalutamide, and St. John's wort [3], [14], [45]–[47].

4.3. Inhibition of CYP3A by CDK4/6 inhibitors

Since all CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, are weak, time-dependent CYP3A inhibitors, there should be caution in case of co-administration with substrates of CYP3A due to high risk of increased exposure and toxicity of these substrates, especially when there is a narrow therapeutic index. The list of sensitive substrates of CYP3A with a narrow therapeutic index includes but is not limited to: Midazolam, fentanyl, dihydroergotamine, ergotamine, primozide, quinidine, tacrolimus, sirolimus, everolimus, cyclosporin, and alfentanil. There might be need for dose reduction of these agents, if concomitant use with CDK4/6 inhibitors cannot be avoided, in order to avoid increased exposure and possible toxicity [3], [14], [45]–[47]. Table 2 summarizes the drug–drug interactions with palbociclib, ribociclib, and abemaciclib.

5. Safety and toxicity profile of CDK4/6 inhibitors: Clinical management of adverse events

The family of CDKs, by improvement in PFS, has proven its efficacy in HR+ and HER2− advanced/metastatic breast cancer [11]. However, like all drugs, the use of CDK4/6 inhibitors demonstrated some adverse events, with neutropenia being the most common [3], [13], [14]. Yet, the side effects associated with chemotherapy are more severe than those induced by CDK4/6 inhibitors. Other adverse events during CDK4/6 inhibitor-based treatment are fatigue, low severity gastrointestinal toxicity, such as vomiting, nausea, and diarrhea, QTc prolongation, hepatobiliary toxicity, pulmonary embolism, and alopecia [45]–[47]. According to the data above, accurate patient monitoring and management of CDK4/6 inhibitors' side effects are recommended [3], [13], [14], [26].

Table 2: Potential drug-drug interactions with cdk4/6 inhibitors.

Drug class	Agent	Treatment	Recommendation
Strong CYP3A* inducers			
Antibiotics	Rifampin, rifabutin, rifapentine	Reduced exposure of CDK4/6 inhibitors	Avoid concomitant administration and consider alternative therapy
Anticonvulsants	Phenytoin, carbamazepine, barbiturates (e.g., phenobarbital)		
Other	Enzalutamide, St. John's wort		
Strong CYP3A inhibitors			
Antibiotics	Clarithromycin, telithromycin	Increased exposure of CDK4/6 inhibitors	Avoid concomitant administration and consider alternative therapy
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole		If co-administration of a strong CYP3A inhibitor cannot be avoided reduce dose of CDK4/6 inhibitor: 75 mg daily for palbociclib, 400 mg daily for ribociclib, and 100 mg twice daily for abemaciclib, reinitiate previous dose after 3–5 half-lives of the inhibitor after discontinuation
Antiretrovirals, protease inhibitors	Atazanavir, darunavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, teleprevir		
Other	Grapefruit or grapefruit juice, nefazodone		
Sensitive CYP3A substrates with a narrow therapeutic index	Midazolam, alfentanyl, fentanyl, cyclosporine, primozide, quinidine, dihydroergotamine, ergotamine, everolimus, sirolimus, tacrolimus	May result in increased exposure of concomitant agent	Close monitoring for signs of toxicity of the concomitant agent, modification of its dose as needed
QT-prolonging agents (only for ribociclib)			
Antiarrhytmics	Amiodarone, disopyramide, procainamide, quinidine, sotalole	QTc prolongation and related consequences	Avoid concomitant administration
Other	Chloroquine, halofantrine, aloperidol, methadone, clarithromycin, moxifloxacin, bepridil, primozide, ondasentrone (IV)†		

*Cytochrome P450
†Intravenous

5.1. Clinical management of hematological adverse events of CDK4/6 inhibitors

5.1.1. Neutropenia

The most common Grade 3/4 adverse events, observed during therapy with CDK4/6 inhibitors plus endocrine therapy, are neutropenia and leukopenia, due to CDK4/6 inhibitors' influence on bone marrow, while anemia and thrombocytopenia are less frequent. CDK6 seems to be of great importance for the promotion of proliferation of hematological precursors. The data above explain the low rates (all grades) of neutropenia seen with abemaciclib, compared to palbociclib and ribociclib, because abemaciclib shows greater selectivity to CDK4 [26]. However, hematological abnormalities associated with CDK4/6 inhibitors can be managed with adequate supportive care [3].

Even though neutropenia induced by CDK4/6 inhibitors is common, it differs mechanistically from the one experienced by patients receiving chemotherapy, because of its rapid reversibility, less severity, no related pancytopenia, and low rates of infection [3], [13], [14]. In particular, it has been observed that 37% of breast cancer patients experienced severe Grade 4 neutropenia, during the first four cycles of chemotherapy, 23% of whom developed subsequent febrile neutropenia (mortality rates of around 5%). On the other hand, Grade 4 neutropenia was observed in less than 10% of patients receiving combination therapy of a CDK4/6 inhibitor and endocrine therapy with low rates of febrile neutropenia: 2.5% in PALOMA-2 (palbociclib+letrozole) [43], 0.9% in PALOMA-3 (palbociclib+fulvestrant) [31], [32], [42], 1.5% in MONALEESA-2 (ribociclib+letrozole) [34], [35], and 0.8% in MONARCH-1 (abemaciclib monotherapy) [38]. Additionally, there is no need for granulocyte-colony-stimulating-factor (GCSF) in neutropenia induced by CDK4/6 inhibitors compared to chemotherapy [14].

Furthermore, neutropenia induced by CDK4/6 inhibitors usually decreases with subsequent cycles. This data suggest that there is no cumulative toxicity. Indeed, it has been shown that CDK4/6 inhibitors induce cell-cycle arrest, resulting in suppression of bone marrow, but without causing apoptosis. In order to explore the mechanism, by which hematological toxicity of palbociclib is caused, an in vitro assay used human bone marrow mononuclear cells (hBMNCs) [45]. The assay demonstrated that palbociclib caused bone marrow suppression through cell-cycle arrest but it did not cause DNA damage or apoptotic cell death. There

was resolution of this suppression after withdrawal of the drug, without any influence on apoptosis and cell viability. In contrast, exposure of the same cells to chemotherapeutic agents demonstrated apoptotic cell death [3].

The hematological toxicity of CDK4/6 inhibitors was measured with the following dosing schedules: Palbociclib 125 mg daily (3 weeks on, 1 week off), ribociclib 600 mg daily (3 weeks on, 1 week off), and abemaciclib 150 mg twice daily continuously. Recommendations concerning dose modification and management of neutropenia induced by CDK4/6 inhibitor-based treatment are as follows:

Ribociclib: Complete blood count (CBC) is indicated at the initiation of therapy, every 2 weeks for the first two cycles, at the beginning of the four subsequent cycles, and then as clinically indicated. In case of Grade 1 or 2 neutropenia (ANC 1000/mm^3 < LLN), no dose adjustment is required. In case of Grade 3 neutropenia (ANC 500-<1000/mm^3), interruption of drug is recommended until recovery to Grade <2, then resume at the same dose, but if toxicity of Grade 3 recurs dose reduction at the next lower level is recommended. If Grade 3 febrile neutropenia occurs, interruption of the drug is recommended and, after resolution to Grade <2, resume at the next lower dose level. If Grade 4 neutropenia (ANC < 500/mm^3) occurs, interruption of the drug is recommended and, after resolution to Grade <2, resume at the next lower dose level [14], [46].

Palbociclib: CBC is indicated prior to first cycle of therapy, every 2 weeks during the first two cycles, and then as clinically indicated. In case of Grade 1 or 2 neutropenia (ANC 1000/mm^3 < LLN), no dose adjustment is required. In case of Grade 3 (ANC 500-<1000/mm^3) neutropenia on Day 1 of the cycle, we interrupt the drug and we repeat CBC in 1 week; when there is recovery to Grade <2, we start the next cycle to the same dose. In case of Grade 3 neutropenia on Day 14 of the first two cycles, we do not interrupt administration of the drug, we repeat CBC on Day 21, and we consider dose reduction if duration of recovery from Grade 3 neutropenia is more than 1 week or if Grade 3 toxicity recurs. If Grade 3 febrile neutropenia occurs, interruption of the drug is recommended and, after resolution to Grade <2, resume at the next lower dose level. If Grade 4 neutropenia (ANC < 500/mm^3) occurs, interruption of the drug is recommended and, after resolution to Grade <2, resume at the next lower dose level [14], [45].

Abemaciclib: CBC is indicated before the initiation of therapy, every 2 weeks for the first two cycles, monthly for another two cycles, and then as clinically indicated. In case of Grade 1 or 2 (ANC 1000/mm^3 < LLN) neutropenia, no dose adjustment is required. In case of Grade 3 (ANC 500-<1000/mm^3) neutropenia dose is suspended until resolution to Grade <2 without reduction of subsequent dose of drug. If Grade 4 neutropenia (ANC < 500/mm^3) occurs, interruption of the drug is recommended and, after resolution to Grade <2, resume at the next lower dose level [14], [47].

Although fever related to neutropenia or sepsis is rare with CDK4/6 inhibitor-based treatment, in order to prevent complications, such as severe myelosuppression related to fever and/or bleeding, infections, including influenza and upper respiratory infections, and for avoidance of Grade 3/4 neutropenia, all patients under CDK4/6 inhibitor-based treatment require adequate monitoring, as mentioned above. Furthermore, neutropenia is considered complicated if it is followed by an infection or fever ≥38.5°C. Conclusively, patient's awareness of any treatment-related side effect is very important. It is mandatory to build a clear communication between the doctor and the patient in order to monitor any possible hematological adverse event during therapy with the combination of a CDK4/6 inhibitor and endocrine therapy [3], [14]. Consultation, such as maintenance of high-standard personal hygiene, avoidance of infectious contacts, and reporting of fever >38.3°C or persistent fever >38°C that lasts more than 1 h, is recommended [13].

5.2. Clinical management of non-hematological adverse events of CDK4/6 inhibitors

5.2.1. QTc prolongation

A notable toxicity of ribociclib is QTc prolongation. Fast and chaotic heartbeats can be caused by this heart rhythm condition, which is called long QT syndrome [48]. There are three clinically relevant categories of QTc prolongation, separately for men and women: For men <430 msec is considered normal, 430–450 msec is considered borderline, and >450 msec is considered prolonged, while for women <450 msec is considered normal, 450–470 msec is considered borderline, and >470 msec is considered prolonged [14]. It has been shown that the CDK4/6 inhibitor ribociclib prolongs the QT interval in a concentration-dependent manner. It is recommended that ribociclib should not be administered in patients who are at risk of developing QTc prolongation [46]. In particular, among patients receiving the combination therapy of ribociclib+letrozole (MONALEESA 2) [43], 3.3% experienced QTc prolongation >480 msec (Grade 2, *n* = 10 [3%] and Grade 3, *n* = 1 [0.3%]). In most of these patients, changes occurred in the first cycle of the combination

therapy and were limited by proactive dose interruption or reduction [34].

Recommendations regarding the management of this toxicity of ribociclib are as follows: Prior to initiating therapy, a baseline electrocardiogram (ECG) is indicated and it should demonstrate a QTcF < 450 msec. Additionally, QT interval should be assessed on Day 14 of cycle one, at the beginning of cycle two, and then as clinically indicated. As far as dose modifications are concerned, the instructions are as follows: If the ECG shows QTcF > 480 msec, ribociclib is interrupted, until resolution to <480 msec. Treatment then resumes at the same dose but, if QTcF > 480 msec recurs, same mode of management follows, but treatment continues at the next lower dose level. If the ECG demonstrates a QTcF > 500 msec, ribociclib is interrupted and treatment resumes at the next lower dose level only when QTcF resolves to <481 msec. Permanent discontinuation of ribociclib is recommended when QTcF interval prolongation is >500 msec or >60 msec change from baseline and in relation with torsades de pointes, signs and symptoms of serious arrhythmia, unexplained syncope, and polymorphic ventricular tachycardia [13], [14]. Since it is well known that a number of medicinal products can cause QT prolongation, great caution should be given in patients under concomitant use of these agents with ribociclib. Moreover, although in most cases the QTcF prolongation under therapy with ribociclib is asymptomatic, patients should be encouraged to report any relative symptom, such as palpitations or fainting episodes. Cautious monitoring is recommended in patients experiencing vomiting and/or diarrhea because levels of electrolytes below normal limits could increase the risk of QTcF prolongation [3], [14], [46], [48].

5.2.2. Elevation of liver enzymes

Asymptomatic increases in liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST) have been observed and reported during combination therapy of a CDK4/6 inhibitor with endocrine therapy. Data from clinical trials for each of the three CDK4/6 inhibitors in patients with HR+/HER2− advanced/metastatic breast cancer are as follows:

Palbociclib: Two cases of hepatic failure and liver-related death were documented under therapy with palbociclib+letrozole combination [43], while 4% of Grade 1/2 ALT increase and 3% of Grade 3 was observed during treatment with palbociclib+fulvestrant [32], [42].

Ribociclib: In ribociclib+letrozole arm, 9.3% and 5.7%, respectively, Grade 3/4 ALT and AST increase was documented with concurrent total bilirubin elevation presented in four patients, but without deaths. Abnormal liver function was completely reversible after treatment discontinuation [34], [35].

Abemaciclib: In the combination treatment with abemaciclib+NSAI, Grade 3 and Grade 4 increases in ALT were 5.8% and 0.6%, respectively, while Grade 3 and Grade 4 increases in AST were 3.8% and 0% [41].

Early identification of abnormal liver function with corresponding elevations in ALT/AST, during treatment combination of a CDK4/6 inhibitor with endocrine therapy, could be prevented via regular liver function tests. Additionally, concurrent use of alternative medications, such as herbal medications, should be avoided due to possible drug–drug interactions and, also, alcohol consumption/abuse is discouraged. Patients with significant hepatic impairment are poor candidates for CDK4/6 inhibitor-based therapy [13], [14].

Recommendations for management and dose modification for hepatobiliary toxicity of ribociclib are as follows:

- Grade 1 (>ULN to 3×ULN) ALT/AST increase: No dose adjustment is required.
- Grade 2 (>3 to 5×ULN) ALT/AST increase: Dose interruption is recommended until recovery to baseline Grade, then resume at same dose level, but, if Grade 2 ALT/AST increase recurs, resume at the next lower dose level.
- Grade 3 (>5 to 20×ULN) ALT/AST increase: Dose interruption is recommended until recovery to baseline Grade, then resume at the next lower dose level, but, if Grade 3 ALT/AST increase recurs, discontinuation of ribociclib is recommended.
- Grade 4 (>20×ULN) ALT/AST increase: Discontinuation of ribociclib is recommended.
- It should be noted that, in case of increase in ALT/AST with concomitant increase of total bilirubin (in absence of cholestasis), discontinuation of ribociclib is recommended, irrespective of baseline Grade [14], [46].

5.2.3. Gastrointestinal toxicities

Gastrointestinal adverse events of CDK4/6 inhibitors include nausea, vomiting, and diarrhea. The first two, nausea and vomiting, should be treated with the administration of antiemetics, such as metoclopramide and serotonine 5-HT3 antagonists. For palbociclib and ribociclib, it is well known that gastrointestinal toxicities occur at low grade. However, extra attention should be given while co-administering antiemetics with ribociclib due to the risk of QT prolongation [3], [13], [14]. In

contrast to palbociclib and ribociclib, abemaciclib has a different profile as far as diarrhea is concerned: In MONARCH-1 (abemaciclib monotherapy) [38] 90% of patients experienced diarrhea of any Grade, 20% of whom had a dose reduction due to Grade 3/4 diarrhea, in MONARCH-2 (abemaciclib+fulvestrant) [39] Grade 1/2 and Grade 3 diarrhea occurred in 73% and 13.4% of patients, respectively, and in MONARCH-3 (abemaciclib+NSAI) [41] diarrhea of any Grade occurred in 81.3% of patients. Despite high levels of diarrhea incidence, there was a quick resolution with a median duration of 7.5 days (Grade 2) and 4.5 days (Grade 3). It should be noted that, in general, diarrhea was experienced within 1 week from abemaciclib initiation. Diarrhea is an adverse event that has to be monitored carefully because it can result in electrolytic abnormalities, serious dehydration, and renal insufficiency, due to loss of fluids and electrolytes. Persistent diarrhea can result not only from CDK4/6 inhibitor administration, but also from other causes, such as bacterial or viral infections. Thus, after infectious causes are ruled out, initial treatment of diarrhea includes hydration and dietary modifications, while anti-motility agents, such as loperamide, diphenoxylate/atropine, and octreotide, can be offered as an extended treatment. Additionally, as diarrhea can increase the risk of infections, its management is very important in order to protect patients, especially those experiencing neutropenia concurrently with the occurrence of diarrhea. Proactive management after the first signs of diarrhea (loose stools) can prevent the complications associated with this side effect [13], [14].

5.2.4. Influence on creatinine levels

Of all three CDK4/6 inhibitors, abemaciclib can reversibly increase serum creatinine levels [14], [47]. Data demonstrated such an increase in 98.3% of patients under treatment combination of abemaciclib+endocrine therapy. Indeed, 1.9% of patients had Grade 3/4 increase of serum creatinine levels. Abemaciclib and its major metabolites are involved in the inhibition of organic cation transporter 2, multidrug, and MATE-2 and MATE-2K. This observation led to the conclusion that the increase in serum creatinine is due to the inhibition of renal transporters that influence the tubular secretion of creatinine. It should be noted that elevated levels of creatinine occurring at the beginning of abemaciclib administration stay elevated during treatment and return to baseline after the end of treatment [47], [49].

5.2.5. Pulmonary embolism

Chemotherapy for cancer with several agents can result in a severe side effect, the thromboembolic event. In particular, thromboembolism is considered one of the leading causes of death in patients under anticancer therapy. The event of thromboembolism has been reported in some rare cases during CDK4/6 inhibitor-based therapy of HR+/HER2− advanced/metastatic breast cancer in combination with endocrine therapy [45]–[47]. Yet, as mentioned above, it is not very common and includes pulmonary embolism, deep vein thrombosis, subclavian vein thrombosis, and vena cava thrombosis. Therefore, it is recommended that all patients should be monitored for possible signs or symptoms of pulmonary embolism, such as chest pain, shortness of breath, hypoxia, rapid breathing, or rapid heart rate. Moreover, reporting of sweating, fainting episodes, light-headedness, or hypotension by patients during combination therapy of CDK4/6 inhibitors with an endocrine agent is crucial since large emboli can be asymptomatic. Additionally, diagnosis of pulmonary embolism can be confirmed with a computed tomography angiography (CTA) or a ventilation perfusion if CTA is contraindicated [3], [13], [14].

5.2.6. Alopecia

Clinical trials regarding the three CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, PALOMA, MONALEESA, and MONARCH, respectively, have shown that the combination of CDK4/6 inhibitors with endocrine therapy has almost twofold higher alopecia rate, of Grade 1/2, compared with endocrine therapy alone [14]. In particular, in PALOMA 2, the possibility of Grade 1/2 alopecia was 32.9% in the combination of palbociclib+letrozole, compared with 15.8% for letrozole alone [43]. In PALOMA 3, there was more than twofold higher alopecia rate in the arm of palbociclib+fulvestrant, compared with fulvestrant alone [32], [42]. In MONALEESA 2, alopecia of Grade 1/2 emerged in 33.2% in the combination therapy with ribociclib+letrozole versus 15.5% with letrozole alone [33]. In MONARCH 2, the combination arm, abemaciclib+fulvestrant, demonstrated 15% Grade 1/2 alopecia, compared with 1.8% in the fulvestrant arm [39]. Finally, in MONARCH 3, 26.6% of patients had alopecia of all Grades, while on abemaciclib+NSAI, compared with 10.6% while on NSAI monotherapy [41]. Tables 3 and 4 summarize the most common adverse events related to CDK4/6 inhibitors and the recommendations about their monitoring.

Table 3: Common side effects of cdk4/6 inhibitors.

Treatment arms	Common side effects (>30% any grade)	Common side effects (>20% Grade 3/4)
Palbociclib		
Palbociclib+letrozole	Neutropenia (80%), leukopenia (39%), fatigue (37%), nausea (35%), arthralgia (33%), alopecia (33%)	Neutropenia (66%), leukopenia (25%)
Palbociclib+fulvestrant	Neutropenia (81%), leukopenia (50%), infections (42%), fatigue (39%), nausea (32%)	Neutropenia (65%), leukopenia (28%)
Ribociclib		
Ribociclib+letrozole	Neutropenia (74%), nausea (52%), infections (50%), fatigue (37%), diarrhea (35%), alopecia (33%), leukopenia (39%)	Neutropenia (59%), leukopenia (21%)
Ribociclib+fulvestrant	Neutropenia (69.6%), nausea (45.3%), fatigue (31.5%)	Neutropenia (46.6%) (Grade 3)
Abemaciclib		
Abemaciclib monotherapy	Leukopenia (91%), diarrhea (90%), neutropenia (88%), anemia (69%), fatigue (65%), nausea (64%), decreased appetite (46%), thrombocytopenia (41%), abdominal pain (39%), vomiting (35%)	Leukopenia (28%), neutropenia (27%), diarrhea (20%)
Abemaciclib+fulvestrant	Diarrhea (86%), neutropenia (46%), nausea (45%), fatigue (40%), abdominal pain (35%)	Neutropenia (23.6%)
Abemaciclib+NSAI	Diarrhea (81.3%), neutropenia (41.3%), fatigue (40.1%), infections and infestations (39.1%), nausea (38.5%)	Neutropenia (59%), leukopenia(21%)

Table 4: monitoring of cdk4/6 inhibitors-associated adverse events.

	Hematologic side effects	Gastrointestinal toxicity	Liver enzyme elevation	Pulmonary embolism	QT prolongation
Signs and symptoms	Shortness of breath, fatigue, increased tendency to bleed and/ or bruise	Diarrhea, nausea, vomiting	Weight loss, jaundice, dark urine, itching, abdominal swelling	Cough, chest pain, shortness of breath, rapid breathing, rapid heart rate	Fainting episodes, palpitations
Clinical assessment	Complete blood count	Electrolyte levels	Liver function tests	Monitoring of patients' symptoms	ECG*
Crucial Time	Cycles 1 and 2, 2 weeks after administration	1 week after abemaciclib administration	During therapy	During therapy	First 4 weeks of treatment
Additional risk factors	Fever, infections, Asian ethnicity, low baseline neutrophil count	Fever, dizziness, abdominal pain	Co-administration of other drugs	Deep vein thrombosis	Diarrhea, vomiting, co-administration of other drugs
Frequency of monitoring	Day 1 of cycles 1 and 2, additional assessment during cycles 1 and 2	During therapy	During therapy	During therapy	During therapy

*Electrocardiogram

6. Conclusion

CDK4/6 inhibitors are innovative drugs that entered the treatment landscape of HR(+)/HER2(−) advanced/ metastatic breast cancer, exhibiting PFS for patients (pre- and postmenopausal) of this subtype of breast cancer in combination with endocrine therapy, compared to endocrine therapy alone. In preclinical and clinical level it has been shown that CDK4/6 inhibitors are all well-tolerated oral agents. Yet, like all medicinal products, there are a number of adverse events related to these agents, with neutropenia being the most common. Other side effects of CDK4/6 inhibitor-based treatment are gastrointestinal and hepatobiliary toxicity, QT prolongation, pulmonary embolism, fatigue, and alopecia. However, the toxicity profile of CDK4/6 inhibitors was proven to be less severe, compared to that of chemotherapy. The key to achieve efficacy and avoid toxicity during CDK4/6 inhibitor-based treatment is early and sufficient monitoring, regular clinical assessments, and reporting of signs or symptoms of any possible adverse event. As time goes, our understanding and knowledge of CDK4/6 inhibitors' mechanism of action and toxicity improves and this will facilitate the use of this highly effective oral treatment in larger populations, reducing the need for chemotherapy in the early treatment lines of metastatic disease, thus allowing for more patients to receive active treatment at home, instead of the hospital. Meanwhile, the ongoing studies will hopefully offer answers to whether these new agents can contribute clinical benefit in other breast cancer subtypes in the near future.

7. Author Contributions

Vasiliki C.Tzelepi, and Eleni T.Timotheadou conceived and designed the study. Vasiliki C.Tzelepi, Aristeidis T.Gogadis, and Christos K. Adamidis provided the study material, collected and assembled the data, analyzed and interpreted the data, and wrote the manuscript. Vasiliki C.Tzelepi, Aristeidis T.Gogadis, Christos K. Adamidis, and Eleni T.Timotheadou approved the manuscript.

8. Disclosures

The authors reported no financial relationships.

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