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Management of Adverse Events Due to Cyclin-Dependent Kinase 4/6 Inhibitors

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Advanced breast cancer · Palbociclib · Ribociclib · Abemaciclib · Cyclin-dependent kinase 4/6 · Endocrine therapy · Cell cycle

Abstract
Cyclin-dependent kinase (CDK) 4/6 inhibitors have become standard of care in the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer. They have been shown to double the efficacy of endocrine-based treatment. Three oral agents are available to date: palbociclib, ribociclib, and abemaciclib. The aim of this article is to give a short overview of the existing efficacy data, to summarize the recommended clinical monitoring procedures for patients under CDK4/6 inhibitors, and to shed light on the clinical management of the most common treatment-emergent adverse events. The hematological class side effect neutropenia as well as non-hematological toxicities (e.g., impaired liver function, prolonged QTc interval, and diarrhea) are discussed. In addition, the current knowledge about relevant drug interactions is reviewed.

Introduction

In January 2015, striking efficacy data for palbociclib, the first-in-class cyclin-dependent kinase (CDK) 4/6 inhibitor, were published for the first time [1]. One month later, based on these data, the US Food and Drug Administration (FDA) approved the first CDK4/6 inhibitor palbociclib (Ibrance®; Pfizer Inc.) for the treatment of postmenopausal women with estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as first-line therapy in combination with letrozole. Meanwhile, CDK4/6 inhibitors have found their way into the standard treatment of women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC). To date, three different CDK4/6 inhibitors have been approved by the European Medical Association (EMA): palbociclib (Ibrance®; Pfizer, New York, NY, USA), ribociclib (Kisquali®; Novartis, Basel, Switzerland), and abemaciclib (Verzenios®; Eli Lilly, Indianapolis, IN, USA). Each of them can be used in combination with an aromatase inhibitor as well as with fulvestrant, either as initial endocrine-based therapy or after disease progression following endocrine therapy.

The aim of this article is to give a condensed overview of existing evidence concerning the clinical characteristics of the three agents with a focus on monitor requirements and management of the most common and clinically relevant adverse events (AEs) during treatment with CDK4/6 inhibitors in breast cancer patients.

Efficacy Data of Endocrine-Based Therapy with CDK4/6 Inhibitors in MBC

There is remarkable consistency in the efficacy data of phase II and phase III trials dealing with first-line CDK4/6 inhibition in advanced/metastatic HR-positive MBC (Table 1). In patients with measurable disease, the objective response rate in all trials was over 50%. In all trials, the

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Table 1. Efficacy of CDK4/6 inhibitors in selected trials in the first-line setting [1–5]

Trial	Phase, treatment	*n*	ORR, %	PFS, months	HR
PALOMA-1	II, letrozol/palbociclib	165	39 vs. 55	10.2 vs. 20.2	0.49
PALOMA-2	III, letrozol/palbociclib	666	44 vs. 55	14.5 vs. 24.8	0.58
MONALEESA-2	III, letrozol/ribociclib	668	37 vs. 53	14.7 vs. NR	0.56
MONARCH-3	III, NSAI/abemaciclib	493	44 vs. 59	14.7 vs. NR	0.54
MONALEESA-7	III, ET+OFS/ribociclib	672	36 vs. 51	13.0 vs. 23.8	0.55

NSAI, nonsteroidal aromatase inhibitor; ET, endocrine therapy; OFS, ovarian function suppression; ORR, objective response rate; PFS, progression-free survival; HR, hazard ratio; NR, not reached.

Table 2. Efficacy of CDK4/6 inhibitors in selected trials in the second-line/endocrine-resistant setting [18]

Trial	Phase, treatment	*n*	ORR, %	PFS, months	HR
PALOMA-3	III, fulv/palbociclib	521	11 vs. 25	4.6 vs. 9.5	0.46
MONARCH-2	III, fulv/abemaciclib	669	21 vs. 48	9.3 vs. 16.4	0.55
MONARCH-1	II, abemaciclib	132	20	6.0	

Fulv, fulvestrant; ORR, objective response rate; PFS, progression-free survival; HR, hazard ratio.

Table 3. Requirements for monitoring complete blood count during the treatment with CDK4/6 inhibitors [9, 19, 20]

	Cycle 1			Cycle 2			Cycles 3–4	Cycles 5–6	Cycles 6+
	day 1	day 14	day 15	day 1	day 14	day 15	day 1	day 1	
Palbociclib	x		x	x		x	x	x	day 1[a]
Ribociclib	x	x		x	x		x	x	as indicated
Abemaciclib	x	x		x	x		x	as indicated	as indicated

[a] For patients who experience a maximum of grade 1 or 2 neutropenia in the first 6 cycles, complete blood counts for subsequent cycles should be monitored every 3 months, prior to the beginning of a cycle, and as clinically indicated.

proportion of patients who had visceral metastases at the time of beginning CDK4/6inhibitor-based therapy was around 60%. The pronounced efficacy of CDK4/6 inhibitors is not limited to postmenopausal patients: In the MONALEESA-7 study, only pre- and perimenopausal patients were randomized to receive endocrine-based therapy alone versus in combination with ribociclib. With a prolongation of the median progression-free survival (PFS) from 13.0 to 23.8 months and a hazard ratio of 0.55, the MONALEESA-7 study results align seamlessly with the results of all other trials [2].

Table 2 summarizes efficacy data of CDK4/6 inhibitors in the endocrine-resistant setting: in the PALOMA-3, MONARCH-2, and MONALEESA-3 studies, the CDK4/6 inhibitors were combined with fulvestrant. Similar to the endocrine-sensitive setting, the addition of a CDK4/6-inhibiting agent lead to a doubling of PFS in all three randomized trials. No conclusions can be drawn from the difference in the response rates of the different studies because other than in the MONARCH-2 and MONALEESA-3 studies, patients who had been treated with first-line chemotherapy were allowed to be included in the PALOMA-3 study. Of note, abemaciclib is the only CDK4/6 inhibitor, which has been tested as a single-agent therapy within a phase II trial and showed efficacy in this setting.

Monitoring Requirements during the Treatment with CDK4/6 Inhibitors

In clinical routine, certain monitoring procedures have been established with the use of CDK4/6 inhibitors. These procedures include regular drawing of the complete blood count with palbociclib, ribociclib, and abemaciclib (Table 3), regular control of liver function tests

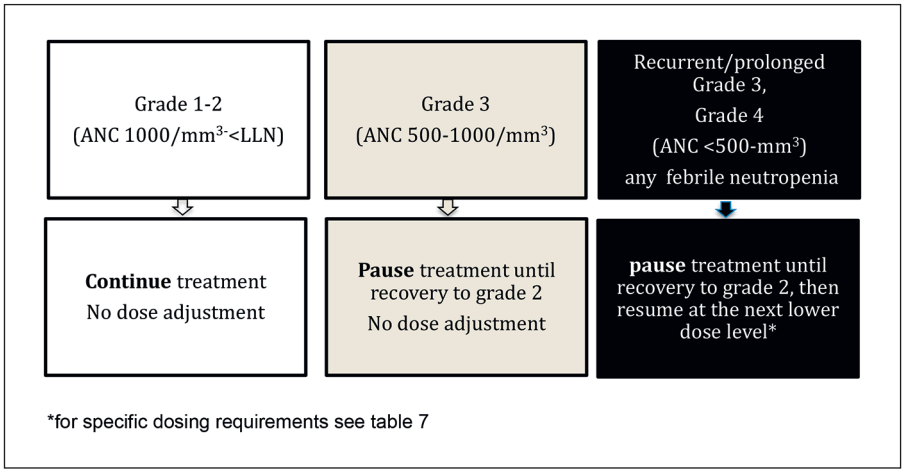

Fig. 1. Management of neutropenia through dose modifications. For specific dosing requirements, see Table 7.

Table 4. Liver function monitoring requirements with ribociclib and abemaciclib [9, 20]

	Cycle 1		Cycle 2		Cycles 3–4	Cycles 5–6	Cycles 6+
	day 1	day 14	day 1	day 14	day 1	day 1	
Ribociclib[a]	x	x	x	x	x	x	as indicated
Abemaciclib	x	x	x	x	x	as indicated	as indicated

[a] If grade ≥2 abnormalities are noted, more frequent monitoring is recommended.

(LFTs) with ribociclib and abemaciclib (Table 4), and regular control of electrocardiogram (ECG) together with monitoring of the QTc interval with ribociclib (Table 5). With ribociclib, appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorous, and magnesium) should also be performed prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated.

Table 5. ECG and QTc monitoring with ribociclib [20]

Before treatment	Cycle 1		Cycle 2		Cycles 3+
	day 1	day 14	day 1	day 14	day 1
x		x	x		as indicated

Management of Neutropenia during the Treatment with CDK4/6 Inhibitors

Neutropenia has been identified as the class side effect of CDK4/6 inhibitors by AE assessment within the PALOMA, MONALEESA, and MONARCH clinical trials [1–5]. Even though grade 3 and grade 4 neutropenia were very common in these trials, the rate of febrile neutropenia did not exceed 2% (Table 6). This is in contrast to the febrile neutropenia rates reported with chemotherapy. For example, in the HERNATA trial where first-line MBC patients had been treated with either docetaxel or vinorelbine, a febrile neutropenia rate up to 36% [6] was reported. The reason for this difference lies in the distinct biological mechanisms being responsible for neutropenia caused by CDK4/6 inhibitors versus cytotoxic chemotherapy agents: it has been shown in vitro that palbociclib causes cell cycle arrest but no death of proliferating neutrophil precursor cells, thus allowing for a rapid recovery of the neutrophil count. Unlike CDK4/6 inhibitors, chemotherapy induces DNA damage and apoptosis of proliferating neutrophil precursors, leading to a delayed recovery of the neutrophil count [7]. Because of these differences, granulocyte colony-stimulating factor should not be used for the management of CDK4/6 inhibitor-induced neutropenia. Neutropenia is managed by dose interruption and dose modification of the CDK4/6 inhibitor while continuing the endocrine agents (Fig. 1, Table 7). If febrile neutropenia occurs, the CDK4/6 inhibitor should be withheld and resumed at the next lower dose level.

If neutropenia coincides with pancytopenia, bone marrow biopsy should be considered to detect possible bone marrow infiltration.

Table 6. Incidence of neutropenia with different CDK4/ inhibitors [9, 19, 20]

AE	Palbociclib		Ribociclib		Abemaciclib	
	any grade	grades 3/4	any grade	grades 3/4	any grade	grades 3/4
Neutropenia	81	65	74	58	41–46	22–27
Febrile neutropenia	2	1	1	NR	<1	

Values are presented as percentages. NR, not reached.

Table 7. Dosing recommendations for CDK4/6 inhibitors in combination with endocrine therapy inhibitors [9, 19, 20]

Dose level	Palbociclib	Ribociclib	Abemaciclib
Recommended starting dose	125 mg daily 3/4 weeks	600 mg daily 3/4 weeks	200 mg twice daily
First dose reduction	100 mg daily 3/4 weeks	400 mg daily 3/4weeks	150 mg twice daily
Second dose reduction	75 mg daily 3/4 weeks	200 mg daily 3/4weeks	100 mg twice daily

Management of Impaired LFTs during the Treatment with CDK4/6 Inhibitors

Early monitoring of LFTs when starting CDK4/6 inhibitor treatment is necessary to identify asymptomatic increase in liver enzymes and to differentiate between CDK4/6 inhibitor toxicity and other reasons such as hepatic progression. Since LFT abnormalities are more common with ribociclib and abemaciclib than with palbociclib, specific recommendations for dose modifications exist with ribociclib and abemaciclib [6, 20].

Management of Qtc Prolongation during the Treatment with Ribociclib

While no clinically significant effects on the QTc interval were observed with palbociclib [8] or abemaciclib [9], ribociclib has been shown to prolong the QTc interval [4]. Treatment with ribociclib should be initiated only in patients with QTcF values <450 ms. ECG should be assessed before initiating the treatment with ribociclib and monitored thereafter according to Table 5. Any abnormality in electrolytes should be corrected before the start of ribociclib treatment. In the event of hypokalemia and/or hypomagnesemia, ribociclib should be interrupted until these are corrected. Management of Qtc prolongation during the treatment with ribociclib is shown in Figure 2. In case of QTcF prolongation during the treatment, more frequent ECG monitoring is recommended.

Management of Diarrhea during the Treatment with Abemaciclib

While palbociclib and ribociclib can be seen as highly selective inhibitors of CDK4 and CDK6, abemaciclib, on a molecular basis, has been shown to have more off-target effects on a variety of other kinases [10]. As a consequence, abemaciclib, unlike palbociclib and ribociclib, can lead to grade 3 diarrhea: in the MONARCH-2 trial, grade 3 diarrhea occurred in 13.4% of the patients treated with abemaciclib [11]. Management of diarrhea should be proactive: at first signs of loose stools, antidiarrheal medication (e.g., loperamide) should be initiated along with an increase in oral fluids. For further management of diarrhea, see Figure 3.

Increase in Serum Creatinine during the Treatment with Abemaciclib

In MONARCH 2, increase in serum creatinine (SCr) was observed in 98.4% of the patients receiving abemaciclib [11]. This increase in SCr due to abemaciclib results from the inhibition of a molecular pump that transports creatinine from the blood to the urine. It occurs within the first 28-day cycle of abemaciclib, remains elevated but stable throughout the treatment period, and is reversible upon treatment discontinuation [12, 13]. Renal function (glomerular filtration rate [GFR]) is not affected by abemaciclib treatment, as are other measures of GFR that do not rely on SCr (such as cystatin C-calculated GFR) [14].

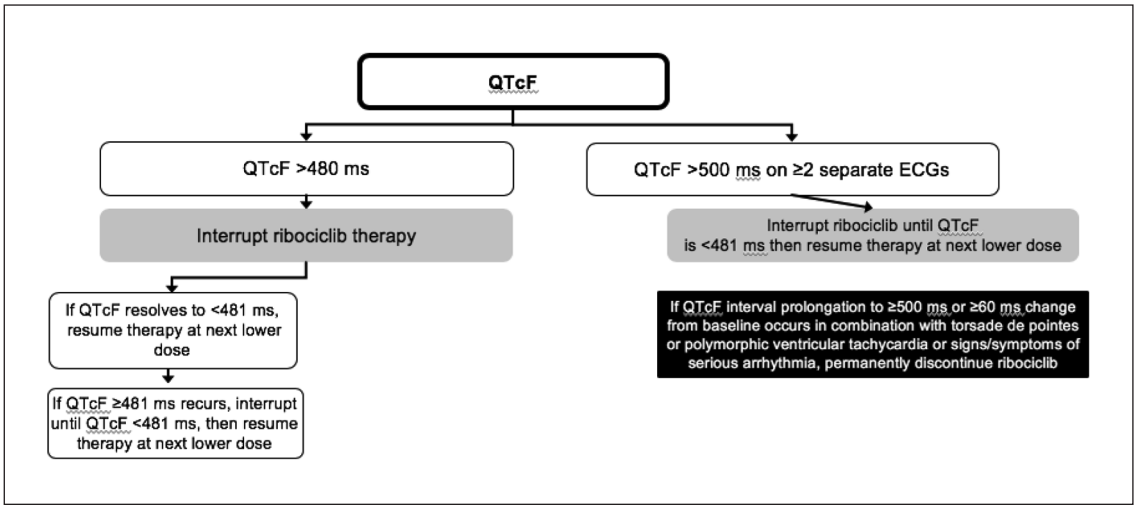

Fig. 2. Management of QTc prolongation during the treatment with ribociclib [21].

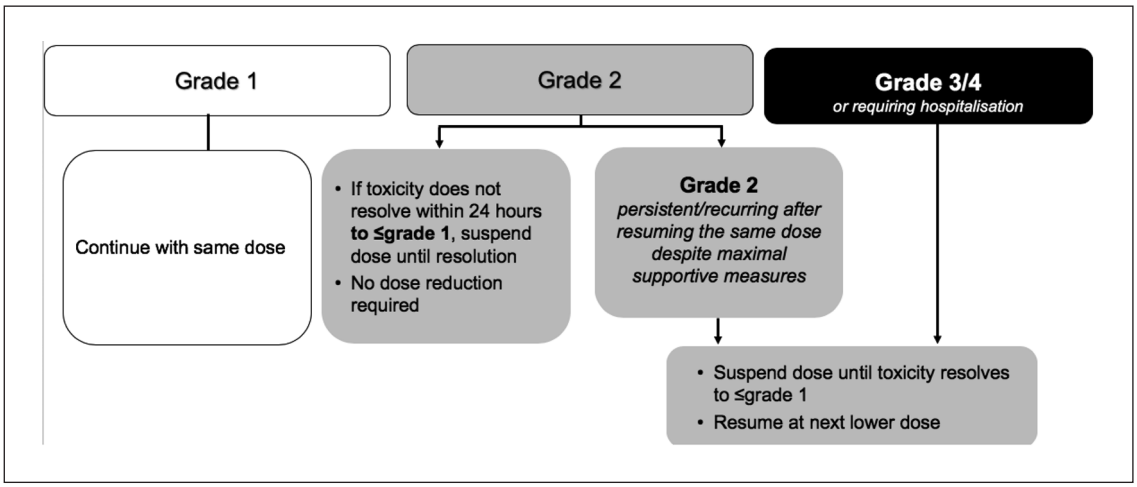

Fig. 3. Management of diarrhea with abemaciclib [5].

If the increase in SCr is progressive or there are other indications for renal injury (e.g., proteinuria), measures of renal function such as cystatin C GFR should be used as an alternative to either SCr or SCr-based calculations of GFR, since creatinine would not be an accurate method to assess renal function.

CDK4/6 Inhibitors and Surgical Procedures or Radiation Therapy

There are no evidence-based recommendations for dose modifications of CDK4/6 inhibitors during times around surgical procedures or radiation therapy. In our own clinical practice, we currently advise to withhold the CDK4/6 inhibitor 1 week before surgery or radiation therapy while continuing the endocrine agent. As soon as the wound-healing process is seen as satisfactory, the CDK4/6 inhibitor can be resumed again. In the case of radiation therapy, we would recommend withholding the CDK4/6 inhibitor for 2–4 weeks after the last irradiation, depending on the size of the irradiated region.

Drug Interactions with CDK4/6 Inhibitors

It is of great importance to take a detailed history of concomitant medications including prescription medicines, over-the-counter drugs, vitamins, and herbal products before starting a patient on CDK4/6 inhibitors. In addition to that, patients must be advised to double-check with their oncologist before starting any new medication.

Palbociclib, ribociclib, and abemaciclib are primarily metabolized by CYP3A and sulfotransferase enzyme SULT2A1. In vivo, they are time-dependent inhibitors of CYP3A.

Agents That May Increase CDK4/6 Inhibitor Plasma Concentrations

Coadministration of a strong CYP3A inhibitor increases the plasma exposure of CDK4/6 inhibitors. Thus, concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole) should be avoided. If coadministration of a strong CYP3A inhibitor cannot be avoided, the dosage of the CDK4/6 inhibitor must be reduced.

Agents That May Decrease CDK4/6 Inhibitor Plasma Concentrations

Coadministration of a strong CYP3A inducer decreases the plasma exposure of CDK4/6 inhibitors. Thus, concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, enzalutamide, or St John's wort) should be avoided.

Drugs That May Have Their Plasma Concentrations Altered by CDK4/6 Inhibitors

The coadministration of CDK4/6 inhibitors and drugs that share the characteristics of being CYP3A substrates with a narrow therapeutic index should be avoided, since this can lead to a cumulation of these drugs and their toxicities. This is for example the case with the (commonly used) statins atorvastatin, lovastatin, and simvastatin. In fact, two cases (one of them being fatal) of statin-induced rhabdomyolysis in patients on palbociclib have been published to date [15, 16].

Drugs That Prolong the QTc Interval

Coadministration of ribociclib with drugs with a known potential to prolong the QTc, such as antiarrhythmic medicines (e.g., amiodarone, disopyramide, procainamide, quinidine, or sotalol) and others (e.g., chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide, or ondansetron), must be avoided to minimize the risk of cardiac arrhythmias. In fact, in the MONALEESA-2 study, one sudden death of a patient who had taken a prohibited concomitant medication with a known risk for QT prolongation (methadone) while being on ribociclib in association with grade 3 hypokalemia and a grade 2 prolongation in the QTcF interval has been reported [17].

Conclusion

With palbociclib, ribociclib, and abemaciclib, a new class of antiproliferative drugs has become standard of care in the endocrine-based treatment of HR-positive, HER2-negative MBC. CDK4/6 inhibitors have led to clinically meaningful improvements in PFS regardless of endocrine sensitivity and menopausal status. On the basis of proper clinical monitoring (e.g., complete blood count, LFTs, ECG, or history of concomitant medications), typical treatment-emergent AEs (e.g., neutropenia, hepatotoxicity, diarrhea, or QTc prolongation) can be clearly identified and safely managed in routine clinical praxis. This makes CDK4/6 inhibitors generally well-tolerated oral agents for our patients with HR-positive, HER2-negative breast cancer.

Disclosure Statement

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