Recommendations for cyclin-dependent kinase 4/6 inhibitor treatments in the context of co-morbidity and drug interactions (Review)

MEHMET TEOMETE¹, DEVRIM CABUK², TANER KORKMAZ³, SELCUK SEBER⁴, OZGE FULYA OZTURK⁵, BIRKAN AVER⁵, ATILA KARAALP⁶ and GUL BASARAN¹

¹Department of Internal Diseases, Division of Medical Oncology, Altunizade Hospital, Acibadem University, Istanbul 34662; ²Department of Internal Diseases, Division of Medical Oncology, Kocaeli University, Izmit, Kocaeli 41380; ³Department of Internal Diseases, Division of Medical Oncology, Acibadem Maslak Hospital, Istanbul 34398; ⁴Department of Internal Diseases, Division of Medical Oncology, Namik Kemal University, Suleymanpasa, Tekirdag 59030; ⁵Department of Medical Oncology, Pfizer Pharmaceuticals, Istanbul 34394; ⁶Department of Pharmacology, The School of Medicine, Biruni University, Istanbul 34010, Türkiye

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Abstract. Breast cancer is most frequently diagnosed among women aged 65-74 years and the prevalence of comorbidities in elderly patients with breast cancer is 32.2%. In addition, polypharmacy is quite common in these patients. Understanding the interaction between breast cancer treatment modalities and comorbidities is important, particularly in elderly patients, as comorbidities affect the choice of appropriate treatment and are independent risk factors for survival. A total of three oral cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i), palbociclib, ribociclib and abemaciclib, notably prolonged progression-free survival when combined with endocrine therapy (ET), compared with ET alone in patients with advanced breast cancer (ABC). The present review article therefore addressed the safety, tolerability and toxicity of CDK4/6i treatment in ABC management, compiled real-world data on how multiple clinical and pharmacological features may affect the choice of these drugs and provided practical recommendations for clinical approaches. Before starting treatment with CDK4/6i drugs, all ongoing medical conditions should be inventorized and re-graded, and examination should be performed for any additional disease that the patient may not be aware of. It is also important to obtain a detailed history of concomitant drugs, including prescription and over-the-counter drugs, vitamins, supplements and herbal

E-mail: mehmetteomete@gmail.com

products. In addition, patients should be advised to consult their oncologist before starting any new medication.

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1. Introduction

Breast cancer is the most common cancer in women, accounting for ~30% of all new cancer cases, ~6% of whom presented with distant metastases in the US in 2020 (1). Female breast cancer is most frequently diagnosed among women aged 65-74 years (median, 62 years) (1) and the prevalence of comorbidities in patients with breast cancer is 32.2% in the elderly (aged >66 years) (2). According to these statistics, polypharmacy is also common in patients with breast cancer. A retsrospective study from Turkiye reported that the frequency of polypharmacy was 50% (n=126) in the non-elderly and 74% (n=74) in the elderly breast cancer patients (3). Therefore, it is important to pay attention to concomitant diseases and polypharmacy during the selection and management of breast cancer treatment, particularly in elderly patients, to prevent or minimize adverse outcomes. Furthermore, it may be possible to improve response and overall survival (OS) rates and maintain the quality of life of patients.

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) are recommended in combination with endocrine therapy (ET)

Correspondence to: Dr Mehmet Teomete, Department of Internal Diseases, Division of Medical Oncology, Altunizade Hospital, Acibadem University, 1 Yurtcan Sokagi, Altunizade, Uskudar, Istanbul 34662, Türkiye

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in patients with advanced breast cancer (ABC). This is based on phase 3 randomized breast cancer trials that have reported notably longer progression-free survival (PFS) compared with ET alone (4). According to an updated analysis of trials, treatment with CDK4/6i plus endocrine therapy resulted in ~33 months of median PFS when used as a first-line treatment and it also provided an advantage as a second-line treatment, where this combination has improved survival for patients who have progressed on prior endocrine therapy alone (5-13). Three oral CDK4/6i agents, palbociclib, ribociclib and abemaciclib, are approved in combination with non-steroidal aromatase inhibitors as a first-line therapy for postmenopausal women with breast cancer (14-16). In OS analyses, ribociclib + an AI demonstrated a significant OS benefit compared with that of the placebo + AI [median, 63.9 vs. 51.4 months; hazard ratio (HR), 0.76; 95% CI, 0.63-0.93; P=0.004] (5). Palbociclib met its primary endpoint of improving PFS in the PALOMA-2 study and the palbociclib + AI group had a notably longer OS compared with that of the placebo + AI group, but the results were not statistically significant (median, 53.9 vs. 51.2 months; HR, 0.956; 95% CI, 0.777-1.177; P=0.3378) (17). Results from studies evaluated the real-world effectiveness of these drugs as a first-line treatment reported that the median OS was significantly longer for patients treated with Palbociclib + AI compared with that of AI recipients (median, 49.1 vs. 43.2 months; HR, 0.76 95% CI, 0.65-0.87; P<0.0001) (18). In final analysis, the median OS was longer for the abemaciclib + AI compared with that of the placebo + AI group (66.8 vs. 53.7 months; (HR, 0.804; 95% CI, 0.637-1.015; P=0.0664), but the results were not statistically significant (19,20). Furthermore, CDK4/6i are a preferred regimen in the first- or second-line treatment with endocrine therapy in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) ABC (5-19).

There is controversy on choosing which CDK4/6i to be selected for which patient profile, as there are no direct comparisons between the agents, with certain differences in the study populations enrolled in the phase 3 randomized studies (16). Therefore, the choice of patient-specific treatments is driven by factors such as endocrine sensitivity, tumor burden, tolerability and the adverse event (AE) profile of CDK4/6i (14-16). Previous meta-analyses suggest that many pharmacological variables, such as concomitant medications related to comorbidities, should also be considered when choosing CDKis for treatment (21).

Understanding the interaction between breast cancer treatment modalities and comorbidities is important, particularly in elderly patients, as comorbidities affect the choice of appropriate treatment and are independent risk factors for survival (22). Of note, the comorbidity burden is a key component of the diagnosis and treatment process, as well as post-cancer care in clinical practice, which is different from clinical trial periods (22). Analyses of pooled study results of CDK4/6is have demonstrated a similar efficacy in older women compared with their younger counterparts, although there were more serious AEs and treatment discontinuations in older patients (23). The aging process alone causes damage and disorders in many organs and systems, which may increase the risk of AEs. Furthermore, most of these patients experience varying degrees of AEs during their treatment due

to comorbid conditions and drug-drug interactions (23). The present review article discusses the safety, tolerability and toxicity of CDK4/6i treatment in ABC management, compiles real-world data on how multiple clinical and pharmacological features may affect the choice of these drugs and provides practical recommendations for clinical approaches.

2. Methodology

During the inception of the present review, which also includes expert opinions, a literature search was performed based on the determination of three main objectives: i) To understand the differences in tolerability profile of CDK4/6i drugs based on their clinical study results and pharmacological properties; ii) to evaluate the potential effects of comorbidities on treatment outcomes in patients with ABC; and iii) to review the current guidelines and other relevant literature that may guide the selection of the appropriate drug for the patient and the treatment management, as well as possible side effects in all these cases.

The main literature search was performed in the English language by searching the MEDLINE® (via the PubMed interface; https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www. webofscience.com/wos/woscc/basic-search), Google Scholar (https://scholar.google.com/) and EMBASE (https://www. embase.com) databases for the 2010-2023 period to use the most recent data. Literature dating back to previous periods was reviewed only for the purpose of evaluating the historical evolution of epidemiological data and relevant treatments. 'CDK4/6 inhibitors and metastatic breast cancer', 'CDK4/6 inhibitors and adverse events', 'comorbidities and breast cancer' and 'CDK4/6 inhibitors and drug interactions' were used as terms for the main literature search. The inclusion criteria were peer-reviewed articles, original study articles, reviews and meta-analysis articles that were published between 2010 and 2023. Articles or case reports that were written in languages other than English were excluded. In addition, articles that were not directly related to toxicities and AEs associated with CDK4/6i used for ABC treatment were not included. The citations of references were reviewed manually. Relevant articles and the most recent related guidelines were also reviewed and suitable articles were determined.

A total of 5 academic oncologists (MT, DC, TK, SS and GB) and 1 pharmacologist (AK), with >20 years experience in the treatment of breast cancer reviewed the publications retrieved from the literature search and identified and evaluated those that would provide insight in relation to the subject matter and the aim of the present review. They subsequently developed recommendations based on the differentiating pharmacological and clinical features of CDK4/6i drugs that may affect the clinical status of patients with ABC.

3. Pharmacological properties, toxicity profile and drugdrug interactions of CDK4/6i treatments

The different pharmacological properties of CDK4/6i are thought to contribute to the different toxicity profiles reported for these agents. The CDK4-cyclin D1 complex is essential for the maintenance of breast cancer growth. Conversely, the CDK6/cyclin D3 complex is particularly relevant for the maturation of hematopoietic stem cells in the bone marrow (24). Palbociclib, ribociclib and abemaciclib inhibit CDK4/6 selectively and reversibly but exhibit different affinities towards CDK4 or CDK6. Abemaciclib is the most potent inhibitor of CDK4 and apart from CDK4 and CDK6, abemaciclib also has mild activity against CDK9, CDK1 and CDK7 (19). CDK9 is an enzyme involved in the regulation of a broad spectrum of transcriptional events, as well as embryogenesis and the cell proliferation process. The activity against CDK9 may partly explain the clinical efficacy of abemaciclib monotherapy demonstrated in the MONARCH-1 and NEXT MONARCH trials (25,26). However, there is no clear comparative data on whether these features affect efficacy or side effects.

Abemaciclib has the shortest half-life among these three agents. It is administered at a dose of 200 mg every 12 h and given continuously without an off-treatment period (25). By contrast, palbociclib and ribociclib are administered for 21 days at standard doses of 125 mg once daily and 600 mg once daily, respectively, followed by 7 days off treatment to reduce the risk of neutropenia.

Ribociclib does not interact with food. Absorption of palbociclib capsules and abemaciclib increases with the consumption of high-fat foods, whilst the absorption of palbociclib capsules decreases with fasting (21). However, palbociclib tablets do not interact with food and abemaciclib interacts only in its prodrug form. As abemaciclib and its active metabolites are most highly bound to plasma proteins, interactions with other drugs that are highly bound to plasma proteins may be important (21).

Palbociclib and abemaciclib easily penetrate the blood-brain barrier due to their lipophilic properties. However, when compared with palbociclib and ribociclib, only abemaciclib may reach and maintain a therapeutic concentration at lower doses. Intracranial activity of abemaciclib was also shown in preclinical studies (21,27-29).

In patients with liver failure, it is recommended to reduce palbociclib and abemaciclib to half the dose in Child-Pugh C and reduce ribociclib to 400 mg in Child-Pugh B and C (21,30). In kidney failure, if creatinine clearance (Crcl) is >15 ml/min, no dose change is required for any of the 3 agents. However, there is insufficient data for palbociclib and abemaciclib in patients with Crcl \leq 15 ml/min or dialysis patients. For ribociclib, the European Medicines Agency and the US Food and Drug Administration (FDA) recommend 200 mg/day in patients with Crcl <15 ml/min (31-33).

None of these drugs have been recommended for pregnant women and breastfeeding mothers (21,32,34). For the elderly, no difference has been found in terms of pharmacological efficacy or side effects (21). However, a study reported that the incidence of grade 3-4 side effects with the use of CDK4/6i was notably higher in patients >75 years of age than in those <75 years of age (88.8 vs. 73.4%). Whilst there is no specific recommendation to start treatment with a lower dose at the outset for patients >75 years of age, more dose reductions have been reported in patients aged \geq 75 years (35). Furthermore, although studies have reported that dose modifications did not affect treatment efficacy, there has not been a subgroup analysis specifically demonstrating how efficacy is affected when the dose is reduced in those aged >75 years, to the best of our knowledge (5-19). It is recommended to adjust the treatment dose by reducing the dose of the drugs according to the degree of the side effect, regardless of age. Detailed pharmacological properties of CDK 4/6i are summarized in Table I.

The most common side effects of CDK4/6i are summarized in Table II from phase 3 studies of the drugs. The most common adverse reactions usually occur in the hematologic system and the gastrointestinal tract. However, the toxicity profiles of these three drugs exhibit certain differences. In general, palbociclib and ribociclib have marked bone marrow toxicity. Abemaciclib has a lower rate of grade 3-4 neutropenia than the other two CDK4/6is. The rate of neutropenia for palbociclib is highest when used with both letrozole and fulvestrant (grade 3-4 neutropenia rate: Palbociclib, 62-66%; ribociclib, 54-59%; abemaciclib, 21-26%) (5-19,36). The reported rate of all-grade thrombocytopenia is higher for abemaciclib, followed by palbociclib, although there is little difference in terms of grade 3-4 AEs (all-grade thrombocytopenia incidence: Palbociclib, 15-19%; ribociclib, 6-8.5%; abemaciclib, 15-36%) (5-19,36). Furthermore, ribociclib has lower anemia rates (5-19,35) and the rate of febrile neutropenia is low (<2%) for all three drugs (36). Gastrointestinal side effects are more prevalent with abemaciclib and in general, loss of taste, abdominal pain and especially diarrhea have been reported more frequently for abemaciclib. However, phase 3 studies have reported the highest rate of hepatotoxicity along with nausea-vomiting, constipation and elevated transaminase levels for ribociclib (5-7). The lowest rates of nausea and vomiting have been reported for palbociclib (<2%). Considering cardiovascular adverse effects, corrected QT (QTc) prolongation has been most frequently reported with ribociclib (3.6-6.2%) (5,6). It has also been reported that the rate of patients with thromboembolic events is higher with abemaciclib (5%), whilst the incidence of hypertension (HT) is more common with ribociclib (5-19). Furthermore, as abemaciclib inhibits renal transporters that mediate tubular secretion of creatinine, serum creatinine elevation has been reported as 10-20% for abemaciclib. However, no data on creatinine elevation appear to be available for the other two agents (5-19,37). The lowest rate of arthralgia has been reported for abemaciclib. The rates of fatigue and alopecia are similar for all three agents. The lowest infection rate has been reported in the group of patients receiving abemaciclib (5-19).

All three agents are primarily metabolized in the liver by cytochrome P450 (CYP)3A (36). Ribociclib also reversibly inhibits CYP1A2 and CYP2E1. Abemaciclib and its major active metabolites have been reported to downregulate CYP mRNAs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4. Furthermore, ~26% of palbociclib is metabolized by sulfotransferase family 2A member 1 (21). However, studies on these enzymes and metabolism of CDK4/6i are not clear, as genetic variations may influence the metabolism and response to CDK4/6i (38). Therefore, more studies are needed in this area (39). However, the present study aimed to guide clinicians in the selection of CDK4/6i, considering the effects of advanced age, comorbidities, concomitant medications and side effects. Therefore, only the CYP3A enzyme is discussed, as it has been reported to be the most influential in the hepatic elimination of CDK4/6i in terms of pharmacodynamic and pharmacokinetic properties.

Drugs or conditions that induce or inhibit the CYP3A enzymes may alter the biotransformation and as a result the

Table I. Pharmacologica	l properties o	of cyclin-	dependent	kinase 4/6	inhibitors	(21, 29-34).
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Item	Palbociclib	Ribociclib	Abemaciclib
Inhibitory effect on kinases	CDK4 = CDK6	CDK4 > CDK6	CDK4 >> CDK6; low potency against CDK1, CDK7 and CDK9
Absolute oral	46	NR	45
bioavailability, %			
Time to maximum	7	5	8
concentration, h			
Half-life, h	25.9	32.6	8.0
Metabolism	CYP3A and SULT2A1	CYP3A4	CYP3A4
Major elimination	74	69	71
route, % in feces			
Food interaction			
Fasting	Increased absorption in capsule form; not affected in tablet form	NA	NA
High-fat meal	Decreased absorption in capsule form; not affected in tablet form	NA	Decreased absorption
BBB penetration	Low	Not penetrated	High
Pro-drug	No	No	Yes: N-desethylabemaciclib (M2), hydroxyabemaciclib (M20) and hydroxy-N-desethylabemaciclib (M18)
Binding protein, %	85	70	96-98
Recommended dosage	125 mg/daily on days 1-21 Q28 with food	600 mg/daily on days 1-21 Q28	200 mg twice daily in monotherapy; 150 mg twice daily in combination with endocrine therapy
Dose adjustment			
Hepatic failure	Child-Pugh A or B: No modifications; Child-Pugh C: 75 mg/day starting dose	Child-Pugh A: No modifications; Child-Pugh B or C: 400 mg/day starting dose	Child-Pugh A or B: No modifications; Child-Pugh C: 150 mg/day starting dose
Renal failure	Crcl >15 ml/min: No dosage adjustment; Crcl ≤15 ml/min: NR; ESRD: NR	Crcl >15 ml/min: No dosage adjustment; Severe: lower starting dose to 400 mg/day (EMA) or 200 mg/day starting dose (FDA) ^a ESRD: NR	Crcl >15 ml/min: No dosage adjustment; Crcl ≤15 ml/min: NR; ESRD: NR
Important drug interactions Use during pregnancy and breastfeeding	CYP3A4 inducers; CYP3A4 inhibitors NR	CYP3A4 inducers; CYP3A4 inhibitors NR	CYP3A4 inducers; CYP3A4 inhibitors NR
Use in elderly	No differences in safety and efficacy	No differences in safety and efficacy	No differences in safety and efficacy

^aOnly studied healthy subjects and noncancer subjects with severe renal impairment. CDK, cyclin-dependent kinase; NR, not recommended; CYP, cytochrome P450; SULT2A1, sulfotransferase family 2A member 1; BBB, blood-brain barrier; Crcl, creatinine clearance; EMA, European Medicines Agency; ESRD, end-stage renal disease; FDA, Food Standards Agency; NA, not affected; Q28, every 28 days.

elimination of CDK4/6i drugs (21). Induction of the CYP3A enzymes has been reported to result in decreased concentrations of CDK4/6i and consequently a lower efficacy of

these drugs. However, inhibition of the CYP3A enzymes has been reported to decrease the metabolism of the drugs, resulting in an increase in their plasma concentration. In this

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	Palboci	iclib + zole	Palboci fulvesi	clib + trant	Riboci letro	clib + zole	Ribocic fulves	clib + trant	Riboci anastro letrozo lh-rh aı	lib + zole/ sle + alog	Abemaci anastro letroz	iclib + zole/ ole	Abemac fulves	iclib + trant
Adverse event	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Hematologic														
Neutropenia	++++	++++	++++	++++	++++	++++	+++++	++++	+++++	++++	+++	++	++++	+
Leukopenia	+++	‡	+++++	++	+++++++++++++++++++++++++++++++++++++++	++	+++	++	+++++++++++++++++++++++++++++++++++++++	++	‡	+	+++++	+
Thrombocytopenia	+	+	++	+	NR	NR	+	+	+	+	+++	+	++	+
Anemia	++	+	++	+	++	+	+	+	+++	+	+++	+	+++	+
Gastrointestinal														
Decreased appetite	+	0	++	+	++	+	‡	0	+	+	‡	+	++++	+
Nausea	+++	0	++++	0	++++	+	+++	+	++++	+	+++	0	++++	+
Vomiting	++	0	++	0	++++	+	+++	+	++++	+	+++	+	++	0
Diarrhea	‡	+	+	0	+++++	+	+++	0	‡	+	++++	+	+++++	++
Transamine elevation	‡	+	+	+	‡	‡	NR	+	‡	+	‡	+	‡	+
Abdominal pain	+	0	+	+	NR	NR	NR	NR	+	+	+++	+	++++	+
Cardiovascular														
Thromboembolism	0	0	+	+	NR	NR	NR	NR	NR	NR	+	0	+	0
QTc prolongation	+	0	0	0	+	0	+	+	+	+	NR	NR	NR	NR
Hypertension	NR	NR	+	+	NR	‡	NR	NR	+	+	NR	NR	NR	NR
Renal														
Blood creatinine elevation	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	+	++	0
Arthralgia	+++	0	++	+	+++++	0	+	0	+++++	+	+	0	++	0
Fatigue	++++	+	+++++	+	+++++	+	++++	+	‡	+	++++	++	+ + +	+
Hot flushes	+	0	++	0	+	0	+	0	++++	0	NR	NR	+	0
Other														
Infections	++++	+	++++	0	+++++	0	+++++	+	+++++	+	+++	+	++++	+
Alopecia	+++	0	++	0	++++	NR	+++++++++++++++++++++++++++++++++++++++	0	+++++	NR	+++	NR	+++++	NR
Adverse event frequency in com corrected QT.	bination with	1 endocrine	therapies in I	ohase 3 trial	ls: 0, <1%; -	+, ≤1-10%;	++, 10-25%	; +++, 25-5	0%; ++++, 5	50-75%; ++	+++, 75-100	%. NR, not	recommend	ed; QTc,

Table II. Clinically significant adverse events of cyclin-dependent kinase 4/6 inhibitors in patients with advanced breast cancer (5-19).

case, side effects and toxicity may be experienced. Table III lists commonly used drugs and drug groups that may inhibit or induce the CYP3A enzyme at moderate and strong levels. Concomitant use of CDK4/6i with a strong CYP3A inducer is not recommended. For the use of moderate CYP3A inducers, it is recommended to monitor drug efficacy and disease control adequately, and concomitant use of CDK4/6i with strong CYP3A inhibitors is not recommended (21,30,40). However, if it is required, the dose of CDK4/6i should be reduced, as indicated in Table IV. For abemaciclib, the dose can be reduced to 50 mg twice daily if adverse effects occur with the administration of 100 mg twice daily (21). For the use of moderate CYP3A inhibitors, it is recommended to monitor the patient in terms of adverse effects and to reduce the dose if necessary (21,30,40). Table III also lists frequently used drugs that may alter the efficacy of CDK4/6i when used concomitantly.

As the metabolism of these drugs slows down in the liver, blood levels of the drugs may increase, leading to toxicity. In this case, strict monitoring and, if necessary, reduction of the dose of concomitantly used drugs is recommended (21,30,40). Finally, drugs that induce QTc prolongation, another condition to be considered in the use of concomitant drugs, are listed by common disease groups in Table IV. These drugs are particularly important for patients using ribociclib, as their concomitant use with ribociclib may cause prolongation of the QT interval and torsade de pointes, which may be fatal. Therefore, their use with ribociclib is not recommended (21,30,40).

4. Prevalence of comorbid conditions in patients with breast cancer and their impact on CDK4/6i treatment outcomes

In a comorbidity analyses study that included a cohort of patients diagnosed with cancer between 1992 and 2005 who resided in 11 Surveillance, Epidemiology and End Results (SEER) areas (Comorbidity Prevalence Among Older Cancer Patients), the prevalence of comorbidities was 32.2% in patients with breast cancer (2). The study also demonstrated that the incidence of mortality due to comorbid diseases increased in parallel to stage, comorbid status and age; and severe comorbidity level was prognostic in all stages and ages. The mortality rate from metastatic breast cancer in those aged 75-84 years was similar between patients without comorbid diseases and those with mild or severe comorbid disease. However, mortality rates from other causes tended to increase in parallel with comorbid disease levels (without comorbid disease, 8.7%; with mild or severe comorbid disease, 13.3 and 21.7%, respectively) (2). According to this report, the most common comorbidities were diabetes mellitus (DM; 14.5%), chronic obstructive pulmonary disease (COPD; 9.5%), congestive heart failure (6.9%), cerebrovascular disease (4.6%), peripheral vascular disease (2.7%) and rheumatologic disease (2.2%; Table IV) (2). Another retrospective study that reviewed the SEER data of ~64,000 patients with breast cancer reported the negative effect of comorbidities on OS in elderly women. Each of the 13 comorbid conditions assessed were associated with decreased OS and increased mortality. Comorbid diseases were classified according to their mortality rate. The study further reported that even if the tumor was diagnosed at an early stage, the survival outcomes in patients with comorbidities were similar to those of patients with a higher tumor stage without any comorbidities (41).

In another study, the effect of comorbidities on health-related quality of life was assessed in patients with breast cancer. Comorbidities were assessed using self-reports and verified by medical record review and the Charlson Comorbidity Index. Quality of life was evaluated using the Short-Form Health Survey. Whilst 73.8% of these patients were reported to have ≥1 comorbidity and 54.7% had 2-4, only 7.4% had 5-8 comorbidities. The most common comorbidities were (HT) (32.8%), arthritis (32.8%), thyroid problems (22.4%), hypercholesterolemia (12.7%) and DM (12.0%). In addition, certain individual comorbidities (namely, HT, arthritis and DM) negatively impacted certain quality of life domains, including physical functioning, general health, bodily pain and vitality (42). Thus, the study reported that comorbid conditions adversely affected not only the prognosis but also the quality of life in patients with breast cancer.

Complications due to surgery, radiotherapy and chemotherapy also cause an increase in comorbidities, regardless of age (2). Local therapies such as breast cancer surgery and radiotherapy may cause persistent pain in the breast area, arm and shoulder, lymphedema and restrictions of arm and shoulder movement. Chemotherapy and endocrine treatment may cause infertility and premature menopause, sexual dysfunction, cognitive problems, fatigue and osteoporosis. Awareness of cardiotoxicity, renal failure, hepatic toxicity, infection, bone marrow suppression, endocrine dysfunctions, thromboembolism, major depression and other psychological symptoms is necessary, since chemotherapeutic agents can damage different organs and systems (43,44). Results from a Canadian study demonstrated that patients with breast cancer had a higher risk of developing new comorbidities than those without cancer. The study evaluated the risk of developing seven comorbidities of interest followed up from the index date (2005-2009) to December 31, 2013. The risks of developing ischemic heart disease, heart failure, depression, DM, osteoporosis and hypothyroidism were higher in patients with breast cancer compared with those with no history of cancer (45). Another study compared the comorbidity scores of 26,213 long-term survivors of breast, colorectal and prostate cancer with a matched control population. The cohort consisted of patients with a mean age of 66.9, 74.1 and 76.1 years for patients with breast, colorectal and prostate cancer, respectively. A high proportion of the population had ≥ 1 comorbid disease and had experienced >5 years of follow-up post-cancer diagnosis. The study also reported an increased rate of heart failure and a notably increased incidence of osteoporosis compared with that of the control, highlighting the risk of developing new comorbid conditions related to late effects of treatment among breast cancer survivors. After accounting for matched groups and additional covariates, an increased rate of coronary artery disease and a marginal increase in the risk of hypothyroidism in survivors of breast cancer was reported (46). In summary, these comorbid conditions may develop as treatment complications in all age populations, but the risk is higher in advanced age.

The strongest prognostic factors predicting relapse or mortality due to breast cancer are patient age, comorbidity,

			CDK4/6i		
Drug group	Commonly used drugs	Palbociclib	Ribociclib	Abemaciclib	Management
Strong CYP3A inducer Antibacterials Anticonvulsants Other	Rifamycin class agents Phenytoin, carbamazepine, primidone, phenobarbital Enzalutamide, St. John's Wort	Reduced exposure to agent. Consider an alternative agent	Reduced exposure to agent. Consider an alternative agent	Reduced exposure to agent. Consider an alternative agent	Concomitant administration should be avoided
Moderate CTF3A inducer Antiviral (HIV, hepatitis) Sterne CVD3A inhibitor	Non-nucleoside reverse transcriptase inhibitors: Nevirapine, efavirenz and etravirine	Monitoring	Monitoring	Monitoring	Monitor the risk of decreased exposure and lack of efficacy
Antiretrovirals/protease inhibitors (HIV, hepatitis) Antifungals	Atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir and telaprevir Itraconazole, ketoconazole, posaconazole	Reduce dose to 75 mg/day	Reduce dose to 400 mg/day	Reduce dose to 100 mg twice a day. If not enough, the dose should be	Concomitant administration should be avoided. Consider alternative therapy or
Antibacterials	and voriconazole Macrolides (erythromycin and clarithromycin)			reduced to 50 mg twice daily	dose reduction
Antibacterials Antifungals Antihypertensives Tyrosine kinase inhibitor Immunosuppressive SSRI Antiarrhythmics	Ciprofloxacin and erythromycin Aprepitant, netupitant, ondansetron and domperidone Fluconazole, itraconazole, isavuconazole, posaconazole, voriconazole and ketoconazole Nifedipine, nicardipine and verapamil Crizotinib and imatinib Cyclosporine Fluvoxamine Dronedarone	Monitoring	Monitoring	Monitoring	Monitor the risk of increased CDKi exposure. Dose reduction can be performed
Commonly used sensitive CYP3A substrates PPI Antihistamines	Lansoprazole and rabeprazole Ebastine and rupatadine	Resulted in increased exposure	Resulted in increased exposure	Resulted in increased exposure to the	Close monitoring of symptoms/dose

Table III. Drug-drug interactions with CDK4/6is (21,30,40).

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Table	

			CDK4/6i		
Drug group	Commonly used drugs	Palbociclib	Ribociclib	Abemaciclib	Management
Angiotensin II receptor blockers	Losartan	to the concomitant. drugs	to the concomitant. drugs	concomitant drugs.	reduction of concomitant drugs is
Beta blockers	Bisoprolol	I	1		recommended
Calcium channel blockers	Dihydropyridines, verapamil and diltiazem				
DPP-4 inhibitors	Saxagliptin and linagliptin				
Metglinides	Repaglinide				
Statins	Simvastatin and atorvastatin				
Antiplatelet	Apixaban, rivaroxaban and clilostazol				
Non-opioid analgesics	Ergotamine and dihydro-ergotamine				
Opioid analgesics	Methadone and fentanyl				
Antidepressants/antipsychotic	Trazodone, mirtazapine, venlafaxine,				
	citalopram, escitalopram and pimozide				
mTOR inhibitors	Everolimus and sirolimusand tacrolimus				
QT interval-prolonging drugs					
Analgesics	Methadone		Prolongation of QT		Coadministration with
Antiarrhythmics	Amiodarone, adenosine, disopyramide,		interval. Torsade de		ribo ciclib should be
	flecainide, ibutilide, procainamide,		pointes		avoided
	propafenone, quinidine and sotalol				
Anticonvulsants	Fosphenytoin				
Antidepressants	Amitriptyline, citalopram, desipramine,				
	doxepin, fluoxetine, imipramine,				
	maprotiline, nortriptyline, paroxetine,				
	sertraline and venlafaxine				
Antihistamines	Clemastine, diphenhydramine and				
	loratadine				
Antibacterials	Clarithromycin erythromycin,				
	gatifloxacin, levofloxacin, moxifloxacin,				
	trimethoprim and sulfamethoxazole				
Antifungals	Fluconazole and ketoconazole				
Antivirals	Foscarnet and ganciclovir				
Antipsychotics	Chlorpromazine, clozapine, haloperidol,				
	quetiapine, risperidone and ziprasidone				
SERM	Tamoxifen				

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			CDK4/6i		
Drug group	Commonly used drugs	Palbociclib	Ribociclib	Abemaciclib	Management
Cardiovascular non-antiarrhythmics 5-HT-antagonists Gastrointestinal agents Migraine agents	Indapamide and probucol Ondansetron and dolasetron Octreotide and droperidol Naratriptan, sumatriptan, rizatriptan and zolmitriptan				
CYP, cytochrome P450; HIV, human imn	nunodeficiency virus; CDKi, cyclin-dependent kini	ase inhibitor; SSRI, selecti	ve serotonin reuptake inł	nibitor; PPI, proton-pump in	hibitor; DPP-4, dipeptidyl

peptidase 4; SERM, selective estrogen receptor modulator.

tumor size, tumor grade, number of involved axillary lymph nodes and possibly HER2 tumor status according to the National Comprehensive Cancer Network guidelines (16). Age and comorbid conditions do not only have prognostic significance in breast cancer but are also important in the choice of treatment. Guidelines recommend that the physician's decision-making process should take concomitant diseases, life expectancy and quality of life into account before initiating the treatment (16,47). However, patients with breast cancer aged 65 years or above, or patients with comorbidities are less frequently involved in the studies and relevant insight is frequently obtained from the retrospective analyses (48). The same applies to research on CDK4/6i; therefore, there are no definite and sufficient recommendations for comorbid conditions when evaluating CDK4/6i treatment options in the current guidelines. Real-world evidence studies may provide certain information on patient populations underrepresented in clinical studies.

5. Treatment management and practical approaches for choosing appropriate CDK4/6i treatments

To reduce the side effects of CDK4/6i treatment, it is necessary to choose the right drug for the right patient, follow the patient appropriately while using the drug and use the right approach in case of toxicity. The most important side effects are neutropenia, diarrhea, QTc prolongation and elevated levels of liver enzymes. Specific monitoring procedures have been established for the use of CDK4/6i drugs in clinical practice. These procedures include a regular complete blood count for palbociclib, ribociclib and abemaciclib, a regular check of liver function tests (LFTs) for ribociclib and abemaciclib and a regular check of electrocardiogram (ECG) along with QTc interval monitoring for ribociclib (49,50). The recommended adverse effect monitoring times for patients using CDK4/6i are listed in Table V.

In the aging process, physiological reserve of multiple systems decreases due to comorbidities, drug interactions and conditions caused by cancer itself (51). However, data evaluating the pharmacokinetics and safety of CDK4/6i drugs in older adults are lacking. Of particular importance, decreased bone marrow reserve seen in elderly patients may increase the risk of myelosuppression, which is a common-class side effect of these drugs (40). Neutropenia is most frequently seen with palbociclib, followed by ribociclib. Therefore, caution should be exercised when using palbociclib and ribociclib. However, the rate of febrile neutropenia is relatively low (<2%) for all three drugs (50). Furthermore, a few points should be noted regarding CDK4/6-induced neutropenia: Although neutropenia is a common side effect of chemotherapeutic agents, neutropenia associated with CDK4/6i arises from the production of neutrophil precursors in the bone marrow through cell cycle arrest without apoptosis and continued proliferation following drug discontinuation. Therefore, it is sufficient to interrupt the drug in the case of bone marrow suppression. There is no need to use granulocyte-colony stimulating factor in the event of neutropenia and resolution of grade 3-4 neutropenia occurs ~7 days after discontinuation of the drug (49,50). Neutropenia is proportional to exposure and generally reduces with subsequent cycles, indicating no cumulative toxicity or

First author, year	Type of study	Scope of the study	Region	Population size	Age, years	Total CMs, %	≥2 CMs, %	Five most common CMs	(Refs.)
Edwards, 2014	Prevalence	Prevalence of comorbidities at the	SU	12,3680	≥66	32.2	9.8	DM, COPD, CHF, CVD and DVD	(2)
Patnaik, 2011	Retrospective	Influence of comorbidities on overall survival among older patients	SU	64,034	75 (mean age)	41.7	13.7	Previous cancer, DM, COPD, CHF and	(41)
Fu, 2015	Prospective	diagnosed with breast cancer Comorbidities at the time of breast	SU	140	56	73.8	62.1	cerebrovascular disease HT, arthritis, TD, HL	(42)
Ng, 2019	Population-based	cancer diagnosis Evaluation of the risk of developing	Canada	13,208	(mean age) ≥50 (majority	NR	NR	and DM CVD, depression, DM,	(45)
Khan, 2011	Database study	comorbidities in survivors of breast cancer Health outcomes associated with	UK	26,213	of women) 66.9	NR	NR	osteoporosis and hypothyroidism CHF, CAD, osteoporosis,	(46)
		treatment among long-term survivors of cancer			(mean age)			hypothyroidism and lymphedema	
CM, comorbidity; HL, hyperlipidem	DM, diabetes mellitus ia; TD, thyroid disease	; COPD, chronic obstructive pulmonary diseas ; CAD, coronary artery disease; NR, not recor	se; CHF, co mmended.	ngestive heart 1	ailure; CVD, cardi	ovascular diseas	e; PVD, periț	oheral vascular disease; HT, hyp	ertension;

Table IV. Comorbid conditions in patients with breast cancer.

	Complete	e blood cour	nt monitoring	Liver	r function m	onitoring	ECG	and QTc n	nonitoring
Drug	Cycle 1	Cycle 2	Other cycles	Cycle 1	Cycle 2	Other cycles	Cycle 1	Cycle 2	Other cycles
Palbociclib	D1, D15	D1, D15	D1	NR	NR	NR	NR	NR	NR
Ribociclib	D1, D14	D1, D14	D1	D1, D14	D1, D14	D1	D14	D1	D1
Abemaciclib	D1, D14	D1, D14	D1	D1, D14	D1, D14	D1	NR	NR	NR
ECG, electroca	rdiogram; QT	c, corrected	QT; NR, not reco	mmended; D	, day.				

Table V. Requirements for monitoring adverse events during treatment with cyclin-dependent kinase 4/6 inhibitors (50,53-56).

need to reduce the dose when restarting if indicated (36,49,50). In addition, it has been reported that dose reduction was not associated with decreased efficacy for palbociclib and ribociclib (50). The management of hematologic AEs is summarized in Table VI.

Prolonged QT syndrome is a heart rhythm condition that can potentially cause rapid, chaotic heartbeats and ribociclib prolongs the QT interval in a concentration-dependent manner. When initiating treatment with ribociclib, patients at risk of QT prolongation or those with QT prolongation before or during cancer therapy should be assessed (52,53). The prolongation of the QTc interval with aging needs to be considered, as it may possibly increase the risk of cardiac AEs in elderly patients receiving ribociclib; therefore, it should not be used in the case of risk (40). Electrolyte changes and drug-drug interactions may also cause QTc prolongation. The combination of ribociclib with tamoxifen has been found to prolong QTc more compared with the combination with nonsteroidal aromatase inhibitors (16 vs. 7%) (53). The FDA has not approved the ribociclib and tamoxifen combination due to concerns about QTc prolongation. In routine practice, patients eligible for ribociclib therapy should be monitored for their cardiac status and concomitant drugs that potentially prolong QTc (54-56). At the beginning of the treatment, patients should be checked with an ECG. Subsequent follow-ups are summarized in Table V and the treatment management is summarized in Table VI.

Gastrointestinal adverse effects are generally seen with abemaciclib. Diarrhea may cause fluid and electrolyte imbalance. Therefore, diarrhea should be carefully monitored. Blood tests can be helpful in detecting changes in electrolyte levels. Abemaciclib may cause a progressive decrease in glomerular filtration rate and renal blood flow may potentially increase the severity of dehydration in older patients with diarrhea or nausea (40,57). Antidiarrheal medications such as loperamide and diphenoxylate/atropine should be used proactively as soon as diarrhea begins in order to prevent complications. Nausea and vomiting should be treated with antiemetics such as metoclopramide and serotonin 5-HT3 antagonists if necessary (50,56).

Liver metabolism decreases with aging (40). Furthermore, hepatic metabolism may be affected by several pharmacological agents that are commonly used for comorbidities. This may result in increased drug exposure and adverse effects, or increased drug metabolism and decreased drug efficacy. In addition, the presence of hepatic metastases is another factor affecting drug metabolism. Early monitoring of LFTs is required when initiating CDK4/6i therapy to identify asymptomatic elevations in liver enzymes and to differentiate CDK4/6i toxicity from other causes, such as hepatic progression. As LFT abnormalities are more common with ribociclib and abemaciclib than with palbociclib, there are specific recommendations for monitoring and dose modifications for ribociclib and abemaciclib, as demonstrated in Tables V and VI (50-56). If a total bilirubin increase is accompanied by an elevation in aspartate aminotransferase or alanine transaminase in the absence of cholestasis, ribociclib should be discontinued irrespective of the baseline grade (56). Hypoalbuminemia due to cachexia or hepatic failure may also affect the serum plasma level of the active metabolite of abemaciclib by altering serum albumin levels (21).

An increase in serum creatinine was reported in 78.4% of patients receiving abemaciclib with fulvestrant or an aromatase inhibitor in phase 3 studies. However, grade 3-4 increases were reported to be very low (1.9%). This indicated there was an inhibition of renal transporters involved in tubular secretion. In general, the increase in creatinine was reported to occur during the first month of treatment and remained stably high. After the end of treatment, the creatinine level returned to the baseline value (56).

Aging and concomitant conditions as well as the cancer itself are highly thrombogenic conditions. Venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism, are serious AEs. VTE has rarely been reported with CDK4/6i, with the incidence of VTE reported to be 5% in the MONARCH3 and MONARCH2 studies, 2% in the PALOMA-3 study and in only 2 cases in the MONALEESA-2 study. Therefore, patients should be monitored for signs and symptoms of thrombosis and pulmonary embolism while on abemaciclib (53,56,57). Direct oral anticoagulants (DOACs) are increasingly being used in cancer patients. Considering that these drugs undergo liver metabolism, the simultaneous administration of CDK4/6 inhibitors (CDK4/6-I) and DOACs needs to be thoroughly discussed, particularly in the absence of data regarding potential pharmacological interactions. Additional information on this crucial topic is strongly needed. Therefore, caution should be taken when using direct acting oral anticoagulants, as concurrent use with CDK4/6i may increase the risk of bleeding (26).

The rate of HT development in patients receiving ribociclib and letrozole combination was reported to be 9.9% (all grades)

		Hematologic side effect		Godmintactinol	Liver enzyme	QT pr	rolongation
Grade	Neutropenia	Thrombocytopenia	Anemia	toxicity: Diarrhea	bilirubin <2x ULN	QTcF >480 msec	QTcF >500 msec
- 0	No dose adjustment required No dose adjustment required	No dose adjustment required No dose adjustment required	No dose adjustment required No dose adjustment required	No dose adjustment required If toxicity does not resolve within 24 h to grade ≤1, stop the treatment. No dose modification is required. Grade 2 that persists/recurs, resume at the next lower dose	No dose adjustment required Dose interruption until recovery to baseline grade, then resume at the same dose level. If grade 2 recurs, resume at the next lower dose level	Interrupt ribociclib treatment if QTcF prolongation resolves to <481 ms. Resume treatment at the same dose level if QTcF ≥481 ms recurs. Interrupt dose until QTcF resolves to <481ms, then resume ribociclib at the next hower dose level	Interrupt ribociclib treatment if QTcF >500 ms on ≥2 separate ECGs (within the same visit). If QTcF prolongation resolves to <481 msec, resume treatment at the next lower dose level. Permanently discontinue ribociclib if QTcF interval prolongation is either >500 msec or
ε	Stop treatment until recovery to grade ≥2. No dose modification is required	Stop treatment until recovery back to 50,000/mm ³ and then resume at the next lower dose level. If recovery to 50,000/mm ³ takes ≥2 weeks, two dose reductions should be	Treatment should be stopped until an improvement to grade ≥ 2 is reached and then resumed at the next lower dose level	Stop treatment until toxicity resolves to grade ≤1. Resume at the next lower dose	Dose interruption until recovery to baseline grade, then resume at the next lower dose level. If grade 3 recurs, discontinue ribociclib		line and associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, unexplained syncope or signs/symptoms of serious arrhythmia
4	Stop treatment until recovery to grade ≥2 and resume at the next lower dose	Same as grade 3	Same as grade 3.	Stop treatment until toxicity resolves to grade ≤1. Resume at the next lower dose	Discontinue ribociclib		

Table VI. Management of common side effects of cyclin-dependent kinase 4/6 inhibitors (50-56).

ECG, electrocardiogra; QTcF, the corrected QT interval by Fridericia; ULN, upper limit normal.

Comorbidities	Palbociclib	Ribociclib	Abemaciclib
Cardiac comorbidities	+++	+	++
Susceptibility to infection and myelosuppression	+	+	+++
Gastrointestinal disease	+++	+++	+
Renal impairment	+++	+++	+
Pulmonary disease	+++	+++	++
Hepatobiliary comorbidities			
Without hypoalbuminemia	+++	+	++
With hypoalbuminemia	+++	++	+
Cachexia	+++	+++	+
Uncontrolled hypertension	++	+	+++
Thromboembolic events	++	+++	+
Arthritis	++	++	+++
Metastatic sites			
Hepatic metastasis			
Without hypoalbuminemia	+++	+	++
With hypoalbuminemia	+++	++	+
Brain metastasis	++	++	+++
Concomitant medication	+++	+	++

Table VII. Cyclin-dependent kinase 4/6 inhibitor recommendations based on the individual condition of patients (16,21,30, 36,40,53-58).

in the MONALEESA-2 study and 6% in the PALOMA-3 study. No relevant data were reported in studies on abemaciclib (5,9,10,13). In a pooled analysis of data from three randomized controlled trials on the combination of CDK4/6i and AI by the FDA (n=1,827), the incidence of grade 3-4 HT with combination therapy was 7.7% in postmenopausal elderly patients (36).

A study evaluating the pulmonary toxicity of CDK4/6i by analyzing the publicly available FDA Adverse Event Reporting System recommended that the rate of CDK4/6i and interstitial lung disease should not be underestimated, and oncologists should be cautious in this regard. The study underscored that patients who were administered abemaciclib reported more interstitial lung disease than those receiving ribociclib and Palbociclib (58). Dose reduction and/or discontinuation of therapy was rarely required in the MONARCH 2 and 3 studies; however, 1/4 patients were treated with steroids and/or antibiotics (58).

Oncologists should take caution whilst using CDKi in patients with several common comorbidities. While there was no specific recommendation for CDK4/6i in the literature for patients with type 2 DM, it is important to know drug-drug interactions related to CDK4/6i in patients with DM and psychiatric disease. In patients administered dipeptidyl peptidase 4 inhibitors and repaglinide, blood glucose imbalances may occur when used with CDK4/6i (21,30,40). Simvastatin and atorvastatin, which are commonly used for the treatment of HL, may interact with CDK4/6i and toxicity of antihyperlipidemics may be observed (21,30,40). Caution should also be exercised when using ribociclib in patients with uncontrolled malignant HT. The administration of angiotensin-converting enzyme inhibitors for patients receiving CDK4/6i treatment appears more appropriate in terms of drug-drug interactions (21,30). Bone and joint pain resulting either from bone metastases or benign causes such as degenerative disease are common in the elderly population, which frequently requires utilization of pain killers (40). Concomitant use of methadone and fentanyl with CDK4/6i may increase serum concentrations of these opioids by causing changes in drug metabolism. In addition, concomitant use also poses a risk in terms of QTc prolongation (21,30).

Neuropsychiatric problems, such as insomnia and depression, are also common in elderly patients (22). In patients using CDK4/6i drugs, it would be appropriate to choose antidepressants such as duloxetine, desvenlafaxine and anxiolytics, such as lorazepam, lormetazepam or clotiazepam, as their interactions are low (21,30). It is not recommended to use CDK4/6i in combination with carbamazepine, phenobarbital or phenytoin in patients with neurological diseases (21,30). Furthermore, certain migraine treatment drugs may cause QTc prolongation. Therefore, caution should be exercised during the treatment of migraines (21,30).

In general, the most common comorbid diseases seen with breast cancer are DM, HT, heart diseases, COPD, osteoporosis, arthritis, cardiovascular disease, depression and hypothyroidism. In light of the available evidence and the current clinical guidelines, recommendations for drug selection based on the patient and CDK4/6i drug characteristics are summarized in Table VII.

6. Discussion

Recent studies on CDK4/6 inhibitors have significantly altered the treatment landscape for HR+ HER2- advanced breast cancer, positioning these drugs ahead of traditional chemotherapy and hormone therapy alone in clinical practice. Among them, abemaciclib has recently been approved in patients with high-risk early breast cancer to be used until completion of 2 years of treatment or until disease recurrence or unacceptable toxicity (15). HR⁺ breast cancer makes accounts for 2/3 of all breast cancers. Most of the patients with HR⁺ HER2⁻ ABC will be administered CDK4/6i drugs during their clinical course. Individualizing cancer therapy is a complex process requiring the complete evaluation of patient- and drug-related factors to prolong survival, minimize toxicity and maintain quality of life in ABC (19). It is therefore important to have foresight regarding how to choose between palbociclib, ribociclib and abemaciclib, which are all effective and tolerable in patients with breast cancer. For instance, the pooled retrospective subgroup analysis of the registration studies that led to approval of the use of these three CDK4/6i drugs for older and younger patients confirmed the PFS benefit of CDK4/6i + ET therapy in all patients regardless of age across trial populations. Therefore, there is no data to support withholding CDK4/6i + ET therapy based on age (35). Pooled data from randomized studies demonstrated that older patients (>75 years) experienced higher toxicity rates, more dose modifications and a greater dose reduction in quality-of-life measures compared with the baseline (35). These findings are supported by real-world clinical outcome and toxicity data from patients with ABC treated with CDK4/6i drugs, as characteristics of unselected real-life patients may not fulfill the eligibility criteria of prospective randomized clinical studies (59,60).

Most patients with breast cancer and advanced age have high rates of comorbidities and concomitant drug use at the onset of oncologic treatment or during treatment. Common comorbidities in patients with breast cancer have been reported to be similar to those in patients without breast cancer in accordance with the age population (2,22). Elderly patients may not be aware of all comorbid diseases due to socioeconomic conditions and cognitive function. Whilst planning treatment, it is necessary for the physician to evaluate the patient holistically before deciding on the choice of treatment. Furthermore, certain anticancer treatments, such as chemotherapy and radiotherapy, may worsen or cause an increased number of comorbidities.

Before starting treatment with CDK4/6i drugs, all concomitant diseases should be accounted for and re-graded, and a full examination should be performed to identify any additional disease that the patient may not be aware of. It is also important to obtain a detailed history of ongoing concomitant medications, including prescription and over-the-counter drugs, vitamins, supplements and herbal products. In addition, patients should be advised to consult their oncologist before starting any new medication.

The present review highlighted the importance of patientand drug-related risks of CDK4/6i treatments in patients with ABC. Awareness of potential risks helps to reduce the complications associated with comorbidities, the prevalence of drug-drug interactions, alleviate drug toxicities and contribute to the effective management of patients with ABC.

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GB made contributions to the design of the work, acted as a moderator during face-to-face discussions, interpreted the collected inputs from other authors, and drafted the manuscript and substantively revised it. MT, DC, TK, SS, OFO, BA and AK made contributions by face-to-face discussions, provided input and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

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