SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 27: 145, 2024

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

MEHMET TEOMETE[1], DEVRIM CABUK[2], TANER KORKMAZ[3], SELCUK SEBER[4], OZGE FULYA OZTURK[5], BIRKAN AVER[5], ATILA KARAALP[6] and GUL BASARAN[1]

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

Received June 25, 2023; Accepted December 12, 2023

DOI: 10.3892/ol.2024.14278

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

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
E-mail: mehmetteomete@gmail.com

Key words: advanced breast cancer, comorbidity, cyclin-dependent kinase 4 and 6 inhibitors, safety, tolerability, toxicity

Contents

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)

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 drug-drug 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 ≤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 ≥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. Pharmacological properties of cyclin-dependent kinase 4/6 inhibitors (21,29-34).

Item	Palbociclib	Ribociclib	Abemaciclib
Inhibitory effect on kinases	CDK4 = CDK6	CDK4 > CDK6	CDK4 >> CDK6; low potency against CDK1, CDK7 and CDK9
Absolute oral bioavailability, %	46	NR	45
Time to maximum concentration, h	7	5	8
Half-life, h	25.9	32.6	8.0
Metabolism	CYP3A and SULT2A1	CYP3A4	CYP3A4
Major elimination route, % in feces	74	69	71
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	CYP3A4 inducers; CYP3A4 inhibitors	CYP3A4 inducers; CYP3A4 inhibitors	CYP3A4 inducers; CYP3A4 inhibitors
Use during pregnancy and breastfeeding	NR	NR	NR
Use in elderly	No differences in safety and efficacy	No differences in safety and efficacy	No differences in safety and efficacy

[a]Only 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

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

	Palbociclib + letrozole		Palbociclib + fulvestrant		Ribociclib + letrozole		Ribociclib + fulvestrant		Ribociclib + anastrozole/ letrozole + lh-rh analog		Abemaciclib + anastrozole/ letrozole		Abemaciclib + fulvestrant	
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 combination with endocrine therapies in phase 3 trials: 0, <1%; +, ≤1-10%; ++, 10-25%; +++, 25-50%; ++++, 50-75%; +++++, 75-100%. NR, not recommended; QTc, corrected QT.

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,

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

Drug group	Commonly used drugs	CDK4/6i			Management
		Palbociclib	Ribociclib	Abemaciclib	
Strong CYP3A inducer					
Antibacterials	Rifamycin class agents	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
Anticonvulsants	Phenytoin, carbamazepine, primidone, phenobarbital				
Other	Enzalutamide, St. John's Wort				
Moderate CYP3A inducer					
Antiviral (HIV, hepatitis)	Non-nucleoside reverse transcriptase inhibitors: Nevirapine, efavirenz and etravirine	Monitoring	Monitoring	Monitoring	Monitor the risk of decreased exposure and lack of efficacy
Strong CYP3A inhibitor					
Antiretrovirals/protease inhibitors (HIV, hepatitis)	Atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir and telaprevir	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 reduced to 50 mg twice daily	Concomitant administration should be avoided. Consider alternative therapy or dose reduction
Antifungals	Itraconazole, ketoconazole, posaconazole and voriconazole				
Antibacterials	Macrolides (erythromycin and clarithromycin)				
Moderate CYP3A inhibitor					
Antibacterials	Ciprofloxacin and erythromycin	Monitoring	Monitoring	Monitoring	Monitor the risk of increased CDKi exposure. Dose reduction can be performed
Antiemetics	Aprepitant, netupitant, ondansetron and domperidone				
Antifungals	Fluconazole, itraconazole, isavuconazole, posaconazole, voriconazole and ketoconazole				
Antihypertensives	Nifedipine, nicardipine and verapamil				
Tyrosine kinase inhibitor	Crizotinib and imatinib				
Immunosuppressive	Cyclosporine				
SSRI	Fluvoxamine				
Antiarrhythmics	Dronedarone				
Commonly used sensitive CYP3A substrates					
PPI	Lansoprazole and rabeprazole	Resulted in increased exposure	Resulted in increased exposure	Resulted in increased exposure to the	Close monitoring of symptoms/dose
Antihistamines	Ebastine and rupatadine				

Table III. Continued.

Drug group	Commonly used drugs	CDK4/6i			Management
		Palbociclib	Ribociclib	Abemaciclib	
Angiotensin II receptor blockers	Losartan	to the concomitant. drugs	to the concomitant. drugs	concomitant drugs.	reduction of concomitant drugs is recommended
Beta blockers	Bisoprolol				
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 interval. Torsade de pointes		Coadministration with ribo ciclib should be avoided
Antiarrhythmics	Amiodarone, adenosine, disopyramide, flecainide, ibutilide, procainamide, 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				

Table III. Continued.

Drug group	Commonly used drugs	CDK4/6i			Management
		Palbociclib	Ribociclib	Abemaciclib	
Cardiovascular non-antiarrhythmics	Indapamide and probucol				
5-HT-antagonists	Ondansetron and dolasetron				
Gastrointestinal agents	Octreotide and droperidol				
Migraine agents	Naratriptan, sumatriptan, rizatriptan and zolmitriptan				

CYP, cytochrome P450; HIV, human immunodeficiency virus; CDKi, cyclin-dependent kinase inhibitor; SSRI, selective serotonin reuptake inhibitor; PPI, proton-pump inhibitor; 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

Table IV. Comorbid conditions in patients with breast cancer.

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 time of first cancer diagnosis	US	12,3680	≥66	32.2	9.8	DM, COPD, CHF, CVD and PVD	(2)
Patnaik, 2011	Retrospective	Influence of comorbidities on overall survival among older patients diagnosed with breast cancer	US	64,034	75 (mean age)	41.7	13.7	Previous cancer, DM, COPD, CHF and cerebrovascular disease	(41)
Fu, 2015	Prospective	Comorbidities at the time of breast cancer diagnosis	US	140	56 (mean age)	73.8	62.1	HT, arthritis, TD, HL and DM	(42)
Ng, 2019	Population-based	Evaluation of the risk of developing comorbidities in survivors of breast cancer	Canada	13,208	≥50 (majority of women)	NR	NR	CVD, depression, DM, osteoporosis and hypothyroidism	(45)
Khan, 2011	Database study	Health outcomes associated with treatment among long-term survivors of cancer	UK	26,213	66.9 (mean age)	NR	NR	CHF, CAD, osteoporosis, hypothyroidism and lymphedema	(46)

CM, comorbidity; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CVD, cardiovascular disease; PVD, peripheral vascular disease; HT, hypertension; HL, hyperlipidemia; TD, thyroid disease; CAD, coronary artery disease; NR, not recommended.

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

	Complete blood count monitoring			Liver function monitoring			ECG and QTc monitoring		
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, electrocardiogram; QTc, corrected QT; NR, not recommended; D, day.

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)

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

	Hematologic side effect					QT prolongation	
Grade	Neutropenia	Thrombocytopenia	Anemia	Gastrointestinal toxicity: Diarrhea	Liver enzyme elevation: Total bilirubin <2x ULN	QTcF >480 msec	QTcF >500 msec
1	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	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 lower 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 >60 msec change from base line and associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, unexplained syncope or signs/symptoms of serious arrhythmia
2	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	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		
3	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 performed	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		
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		

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

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

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	+++	+	++

+++, strong recommendation; ++, moderate recommendation; +, low recommendation.

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 patient- and 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.

Acknowledgements

Manuscript editing and revision assistance was provided by Dr Ferda Kiziltas, Medical Affairs Manager at Remedium Consulting Group (Izmir, Türkiye).

Funding

The present review was funded by Pfizer.

Availability of data and materials

Not applicable.

Authors' contributions

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

BA and OFO are employees of Pfizer, who provided funding for the present study.

References

1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2020. CA Cancer J Clin 70: 7-30, 2020.
2. Edwards BK, Noone AM, Mariotto AB, Simard EP, Boscoe FP, Henley SJ, Jemal A, Cho H, Anderson RN, Kohler BA, *et al*: Annual report to the nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 120: 1290-1314, 2014.
3. Topaloğlu US and Özaslan E: Comorbidity and polypharmacy in patients with breast cancer. Breast Cancer 27: 477-482, 2020.
4. Gao JJ, Cheng J, Bloomquist E, Sanchez J, Wedam SB, Singh H, Amiri-Kordestani L, Ibrahim A, Sridhara R, Goldberg KB, *et al*: CDK4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: A US food and drug administration pooled analysis. Lancet Oncol 21: 250-260, 2020.
5. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Hart L, Campone M, Petrakova K, Winer EP, Janni W, *et al*: LBA17 overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Ann Oncol 32 (suppl_5): S1283-S1346, 2021.

6. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M, *et al*: Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol 36: 2465-2472, 2018.
7. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M, *et al*: Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med 382: 514-524, 2020.
8. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, Hurvitz SA, Chow L, Sohn J, Lee KS, *et al*: Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): A randomised phase 3 trial. Lancet Oncol 19: 904-915, 2018.
9. Sledge GW Jr, Toi M, Neven P, Soh J, Inoue K, Pivo X, Burdaeva O, Okera M, Masud N, Kaufman PA, *et al* MONARCH 2: Abemaciclib in combination with fulvestrant in women With HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 35: 2875-2884, 2017.
10. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, Park IH, Trédan O, Chen SC, Manso L, *et al*: MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 35: 3638-3646, 2017.
11. Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, Frenzel M, Hardebeck MC, Cox J, Barriga S, *et al*: MONARCH 3 final PFS: A randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer 17: 5, 2019.
12. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, *et al*: Palbociclib and Letrozole in advanced breast cancer. N Engl J Med 375: 1925-1936, 2016.
13. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, *et al* Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 379: 1926-1936, 2018.
14. Finn RS, Rugo HS, Dieras VC, Harbeck N, Im SA, Gelmon KA, Walshe JM, Martin M, Gregor MCM, Bananis E, *et al*: Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2-ABC): Analyses from PALOMA-2. J Clin Oncol 40 (17_suppl): LBA1003-LBA1003, 2022.
15. Rugo HS, Brufsky A, Liu X, Li B, McRoy L, Chen C, Layman RM, Cristofanilli M, Torres MA, Curigliano G, *et al*: Real-world study of overall survival with palbociclib plus aromatase inhibitor in HR+/HER2- metastatic breast cancer. NPJ Breast Cancer 8: 114, 2022.
16. Goetz M, Toi J, Huober J, Sohn J, Tredan O, Park IH, Campone M, Chen SC, Sanchez LM, Paluch-Shimon S, *et al*: MONARCH 3: Interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2- advanced breast cancer (ABC). M.P. Ann Oncol 33 (suppl_7): S808-S869, 2022.
17. Munzone E, Pagan E, Bagnardi V, Montagna E, Cancello G, Dellapasqua S, Iorfida M, Mazza M and Colleoni M: Systematic review and meta-analysis of post-progression outcomes in ER+/HER2- metastatic breast cancer after CDK4/6 inhibitors within randomized clinical trials. ESMO Open 6: 100332, 2021.
18. Onesti CE and Jerusalem G: CDK4/6 inhibitors in breast cancer: Differences in toxicity profiles and impact on agent choice. A systematic review and meta-analysis. Expert Rev Anticancer Ther 21: 283-298, 2021.
19. National Comprehensive Cancer Network (NCCN): Breast Cancer. Clinical Practice Guidelines in Oncology-version 1. NCCN, 2023.
20. Goetz M: LBA15 - MONARCH 3: Interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2- advanced breast cancer (ABC). Ann Oncol 33 (Suppl 7): S808-S869, 2022.
21. Roncato R, Angelini J, Pani A, Cecchin E, Sartore-Bianchi A, Siena S, De Mattia E, Scaglione F and Toffoli G: CDK4/6 Inhibitors in breast cancer treatment: Potential interactions with drug, gene, and pathophysiological conditions. Int J Mol Sci 21: 6350, 2020.
22. Danese MD, O'Malley C, Lindquist K, Gleeson M and Griffiths RI: An observational study of the prevalence and incidence of comorbid conditions in older women with breast cancer. Ann Oncol 23: 1756-1765, 2012.
23. Omarini C, Piacentini F, Sperduti I, Barbolini M, Isca C, Toss A, Cortesi L, Barbieri E, Dominici M and Moscetti L: Combined endocrine approaches vs. endocrine therapy alone as first line treatment in elderly patients with hormone receptor-positive, HER2 negative, advanced breast cancer: To prescribe for the patient or the physician? A meta-analysis of phase II and III randomized clinical trials. BMC Cancer 20: 418, 2020.
24. Fry DW, Harvey PJ, Keller PR, Elliott WL, Meade M, Trachet E, Albassam M, Zheng X, Leopold WR, Pryer NK and Toogood PL: Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther 3: 1427-1438, 2004.
25. Marra A and Curigliano G: Are all cyclin-dependent kinases 4/6 inhibitors created equal? NPJ Breast Cancer 5: 27, 2019.
26. Hamilton E, Cortes J, Ozyilkan O, Chen SC, Petrakova K, Manikhas A, Jerusalem G, Hegg R, Huober J, Chapman SC, *et al*: NextMONARCH: Abemaciclib monotherapy or combined with tamoxifen for metastatic breast cancer. Clin Breast Cancer 21: 181-190.e2, 2021.
27. Nguyen LV, Searle K and Jerzak KJ: Central nervous system-specific efficacy of CDK4/6 inhibitors in randomized controlled trials for metastatic breast cancer. Oncotarget 10: 6317-6322, 2019.
28. Anders CK, Le Rhun E, Bachelot TD, Yardley DA, Awada A, Conte PF, Kabos P, Bear M, Yang Z, Chen Y and Tolaney SM: A phase II study of abemaciclib in patients (pts) with brain metastases (BM) secondary to HR+, HER2 metastatic breast cancer (MBC). J Clin Oncol 37: 1017, 2019.
29. Tolaney SM, Sahebjam S, Le Rhun E, Bachelot T, Kabos P, Awada A, Yardley D, Chan A, Conte P, Diéras V, *et al*: A phase II study of abemaciclib in patients with brain metastases secondary to hormone receptor-positive breast cancer. Clin Cancer Res 26: 5310-5319, 2020.
30. Fogli S, Del Re M, Curigliano G, van Schaik RH, Lancellotti P and Danesi R: Drug-drug interactions in breast cancer patients treated with CDK4/6 inhibitors. Cancer Treat Rev 74: 21-28, 2019.
31. KISQALI®(ribociclib). Highlights of Prescribing Information. 2020. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209092s004lbl.pdf (accessed on 14 August 2020).
32. Committee for Medicinal Products for Human Use (CHMP). KISQALI®(ribociclib) EPAR Assessment Report Variation. Available online: https://www.ema.europa.eu/en/documents/variationreport/kisqali-h-c-4213-ii 0004-epar-assessment-report-variation_en.pdf (accessed on 31 August 2020).
33. Ji Y, Yartsev V, Quinlan M, Serra P, Wang Y, Chakraborty A and Miller M: Justifying ribociclib dose in patients with advanced breast cancer with renal impairment based on PK, safety, and efficacy data: An innovative approach integrating data from a dedicated renal impairment study and oncology clinical trials. Clin Pharmacokinet 62: 493-504, 2023.
34. Committee for Medicinal Products for Human Use (CHMP). VERZENIOTM (abemaciclib) EPAR Assessment Report. Available online:https://www.ema.europa.eu/en/documents/assessment-report/verzenios-eparpublic-assessment-report_en.pdf (accessed on 31 August 2020).
35. Howie LJ, Singh H, Bloomquist E, Wedam S, Amiri-Kordestani L, Tang S, Sridhara R, Sanchez J, Prowell TM, Kluetz PG, *et al*: Outcomes of older women with hormone receptor-positive, human epidermal growth factor receptor-negative metastatic breast cancer treated with a CDK4/6 inhibitor and an aromatase inhibitor: An FDA pooled analysis.J Clin Oncol 37: 3475-3483, 2019.
36. Kassem L, Shohdy KS, Lasheen S, Abdel-Rahman O and Bachelot T: Hematological adverse effects in breast cancer patients treated with cyclin-dependent kinase 4 and 6 inhibitors: a systematic review and meta-analysis..Breast Cancer 25: 17-27, 2018.
37. Matsunuma R: Significance of renal function monitoring during treatment with abemaciclib. J Clin Exp Nephrol Vol 5: 81, 2020.
38. Flaherty KT, Lorusso PM, Demichele A, Abramson VG, Courtney R, Randolph SS, Shaik MN, Wilner KD, O'Dwyer PJ, Schwartz GK, *et al*: Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. Clin Cancer Res 18: 568-576, 2012.
39. Zhu Z and Zhu Q: Differences in metabolic transport and resistance mechanisms of Abemaciclib, Palbociclib, and Ribociclib. Front. Pharmacol 14: 1212986, 2023.

40. Battisti NML, De Glas N, Sedrak MS, Loh KP, Liposits G, Soto-Perez-de-Celis E, Krok-Schoen JL, Menjak IB and Ring A: Use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in older patients with ER-positive HER2-negative breast cancer: Young international society of geriatric oncology review paper. Ther Adv Med Oncol 10: 1758835918809610, 2018.
41. Patnaik JL, Byers T, Diguiseppi C, Denberg TD and Dabelea D: The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 103: 1101-1111, 2011.
42. Fu MR, Axelrod D, Guth AA, Cleland CM, Ryan CE, Weaver KR, Qiu JM, Kleinman R, Scagliola J, Palamar JJ and Melkus GD: Comorbidities and quality of life among breast cancer survivors: A prospective study. J Pers Med 5: 229-242, 2015.
43. Ewertz M and Jensen AB: Late effects of breast cancer treatment and potentials for rehabilitation. Acta Oncol 50: 187-193, 2011.
44. Common Toxicity Criteria, Version 2.0. Publish Date: April 30, 1999. Cancer Therapy EvaluationProgram. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf.
45. Ng HS, Vitry A, Koczwara B, Roder D and McBride ML: Patterns of comorbidities in women with breast cancer: A Canadian population-based study. Cancer Causes Control 30: 931-941, 2019.
46. Khan NF, Mant D, Carpenter L, Forman D and Rose PW: Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: A database study. Br J Cancer 105 Suppl 1 (Suppl 1): S29-S37, 2011.
47. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, Barrios CH, Bergh J, Bhattacharyya GS, Biganzoli L, *et al*: 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 31: 1623-1649, 2020.
48. Varghese F and Wong J: Breast cancer in the elderly. Surg Clin North Am 98: 819-833, 2018.
49. Spring LM, Zangardi ML, Moy B and Bardia A: Clinical management of potential toxicities and drug interactions related to cyclin-dependent kinase 4/6 inhibitors in breast cancer: Practical considerations and recommendations. Oncologist 22: 1039-1048, 2017.
50. Ettl J: Management of adverse events due to cyclin-dependent kinase 4/6 inhibitors. Breast Care (Basel) 14: 86-92, 2019.
51. Vallet-Regí M, Manzano M, Rodriguez-Mañas L, López MC, Aapro M and Balducci L: Management of cancer in the older age person: An approach to complex medical decisions. Oncologist 22: 335-342, 2017.
52. Hart LL, Bardia A, Beck JT, Chan A, Neven P, Hamilton EP, Sohn J, Sonke GS, Bachelot T, Spring L, *et al*: Impact of ribociclib (RIB) dose modifications (mod) on overall survival (OS) in patients (pts) with HR+/HER2- advanced breast cancer (ABC) in MONALEESA(ML)-2. J Clin Oncol 40 (16_suppl): S1017-S1017, 2022.
53. Murphy CG: The role of CDK4/6 inhibitors in breast cancer. Curr Treat Options Oncol 20: 52, 2019.
54. Cazzaniga ME, Danesi R, Girmenia C, Invernizzi P, Elvevi A and Uguccioni M; NetworkER+: Management of toxicities associated with targeted therapies for HR-positive metastatic breast cancer: A multidisciplinary approach is the key to success. Breast Cancer Res Treat 176: 483-494, 2019.
55. Sammons SL, Topping DL and Blackwell KL: HR+, HER2- advanced breast cancer and CDK4/6 inhibitors: Mode of action, clinical activity, and safety profiles. Curr Cancer Drug Targets 17: 637-649, 2017.
56. Thill M and Schmidt M: Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer. Ther Adv Med Oncol 10: 1758835918793326, 2018.
57. Spring LM, Wander SA, Andre F, Moy B, Turner NC and Bardia A: Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: Past, present, and future. Lancet 395: 817-827, 2020.
58. Raschi E, Fusaroli M, Ardizzoni A, Poluzzi E and De Ponti F: Cyclin-dependent kinase 4/6 inhibitors and interstitial lung disease in the FDA adverse event reporting system: A pharmacovigilance assessment. Breast Cancer Res Treat 186: 219-227, 2021.
59. Caillet P, Pulido M, Brain E, Falandry C, Desmoulins S, Ghebriou D, Soubeyran P, Paillaud E, Rifi N, Vauthier JM, *et al*: PALOMAGE, a French real-world cohort of elderly women beyond age 70 with advanced breast cancer receiving palbociclib: Baseline characteristics and safety evaluation. J Clin Oncol 39 (15_suppl): 1012-1012, 2021.
60. Fountzilas E, Koliou GA, Vozikis A, Rapti V, Nikolakopoulos A, Boutis A, Christopoulou A, Kontogiorgos I, Karageorgopoulou S, Lalla E, *et al*: Real-world clinical outcome and toxicity data and economic aspects in patients with advanced breast cancer treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors combined with endocrine therapy: The experience of the Hellenic cooperative oncology group. ESMO Open 5: e000774, 2020.