Original Article

Oral adverse effects of CDK4/6 inhibitors among breast cancer patients: a systematic review and meta-analysis

Quanyi Long[1], Xiaomin Li[1], Gonghua Wu[2], Jia Zhang[1], Hongjiang Li[1]

[1]Department of Breast Surgery, West China Hospital, Sichuan University, Chengdu, China; [2]Department of Biostatistics, School of Public Health, Sun Yat-Sen University, Guangzhou, China

Contributions: (I) Conception and design: Q Long, H Li; (II) Administrative support: H Li; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Q Long, G Wu, J Zhang; (V) Data analysis and interpretation: G Wu, X Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hongjiang Li. Department of Breast Surgery, West China Hospital, Sichuan University, No.37 Guoxue Alley, Wuhou District, Chengdu, China. Email: lihongjiang@sohu.com.

Background: Cyclin-dependent kinase (CDK) inhibitors are widely used to treat hormone receptor-positive (HR+) breast cancer due to their efficient performance in improving survival outcomes. Although the side effects of these agents on the hematological and gastrointestinal systems have attracted significant attention, the adverse effects that have direct impacts on patients' quality of life, such as stomatitis, have not been well explored to date.

Methods: A systematic literature search was conducted in the PubMed, Google Scholar, European Society of Medical Oncology (ESMO), and American Society of Clinical Oncology databases. Phase 2 and 3 randomized trials on CDK4/6 inhibitors (CDK4/6Is) were identified and used in the meta-analysis based on the completeness of their safety data.

Results: Of the 904 records screened, 40 studies were considered relevant. Six studies were used in the meta-analysis, with a total of 2,980 patients in the safety population. The pooled relative risk (RR) and risk difference (RD) for any-grade stomatitis were 2.02 (95% CI: 1.65–2.48) and 0.10 (95% CI: 0.05–0.15), respectively. In the subgroup analysis, higher RRs were observed among patients receiving letrozole as basic endocrine therapy (ET) (8.50, 95% CI: 2.22–32.57) or palbociclib-containing regimens (2.44, 95% CI: 1.88–3.18), whereas the RDs showed no significant difference

Discussion: All CDK4/6Is, especially palbociclib, could increase the risk of developing stomatitis among patients with breast cancer. Prevention and management of CDK4/6Is-related stomatitis may effectively reduce its secondary impacts. Due to the lack of individual-level data, some important personal confounding variables could not be controlled. Besides, the explanations of the secondary effects of stomatitis in this study were only based on the literature and professional knowledge. The specific quantitative impacts on patient quality of life and compliance require further questionnaire investigation. More in-depth individual-level data are needed to quantify the effect of stomatitis on patients' quality of life and treatment compliance.

Keywords: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6Is); palbociclib; breast cancer; stomatitis

Submitted Apr 07, 2021. Accepted for publication Jun 15, 2021.
doi: 10.21037/apm-21-1156
View this article at: https://dx.doi.org/10.21037/apm-21-1156

Introduction

Breast cancer is one of the most challenging tumors in women worldwide and has the highest cancer-related incidence and mortality (1). More than 1.5 million new cases are reported globally every year, over 80% of which are hormone receptor-positive (HR+) or human epidermal growth factor 2 positive (HER2+) (2). Endocrine therapy (ET) has become the standard first-line treatment, however

the probability of developing de novo and acquired resistance increases markedly after 2–3 years of ET treatment (2,3). At this point, patients are often destined to receive chemotherapy, which has little activity and a high risk of toxicity.

In recent years, considerable efforts have been made to slow the pace of acquiring ET resistance and delaying the introduction of chemotherapy. One of the most critical discoveries is the cyclinD-CDK4/6-retinoblastoma protein (Rb) pathway (4), which initiates the transition from the G1 phase to the S phase. Overexpression of cyclin D1 and activation of CDK4/6 in this pathway can drive breast cancer proliferation, and thus, inhibition of this mechanism can effectively delay cancer progression.

CDK4/6 inhibitors (CDK4/6Is), including palbociclib, ribociclib, and abemaciclib, are agents that restrain the cell phase transition and solve the ET resistance problem. Numerous randomized controlled trials (RCTs) have revealed a significant increase in progression free survival (PFS) and overall survival (OS) with the addition of CDK4/6Is to ET (5-7). The adverse effects of these agents have also attracted widespread attention, especially their hematological and gastrointestinal toxicity (8-10). However, other frequently encountered adverse events that have direct impacts on patients' quality of life are rarely studied. Specifically, these three oral inhibitors may have a high risk of triggering stomatitis due to both physical and pharmacological stresses. Nevertheless, patients receiving ET alone rarely suffer from stomatitis. Therefore, it is important to assess whether the combination of CDK4/6Is with ET increases this risk and minimizes the potential safety advantage of single-agent ET.

For this reason, we performed a systematic review and meta-analysis of RCTs to explore the added toxicity of stomatitis in patients treated with CDK4/6Is plus ET versus ET alone.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1156).

Methods

Search strategy and selection criteria

We conducted a systematic literature search on the *PubMed* database using the keywords 'Palbociclib OR Ribociclib OR Abemaciclib OR CDK 4/6 inhibitors' AND 'breast cancer'. Additional searches were performed in Google Scholar and databases of major oncology congresses from January 2014 to July 2020, including the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology. Non-English papers were not in the search field, and only the most recent report was retained if duplicate cases existed. A bibliography scan was also conducted to identify any missing relevant articles. This was implemented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (11).

We included trials that satisfied the following criteria: (I) phase 2 or 3 RCTs recruiting patients with breast cancer; (II) patients who had been randomly assigned to a CDK4/6 or control group; and (III) the rate of stomatitis was given. We excluded papers for the following reasons: (I) phase 1 trials or non-randomized trials; and (II) insufficient reporting of the safety data.

Data extraction

According to a standardized protocol, Quanyi Long and Gonghua Wu independently collected the following information from each eligible study: name of the first author, year of publication, study phase, treatment arms, number of patients available for analysis, hormone type of the breast cancers, and the number of patients who developed any-grade and high-grade (grade 3 or 4) stomatitis.

Statistical analysis

The 'meta' and 'metafor' packages in R software (version 3.6.2) were used to perform data analysis and generate the plots. A P value less than 0.05 was defined as significant. The I^2 statistic and Cochran's Q statistics were used to explore the potential heterogeneity among the studies. The pooled relative risk (RR) and risk difference (RD) with 95% CI were obtained from the fixed-effect and random-effect models using the Mantel-Haenszel method. Subgroup analyses for RRs of stomatitis were conducted according to the different CDK4/6Is and different types of ET. Potential publication bias was not assessed because of the inadequate number of included trials to properly explore with a funnel plot or more advanced assessments.

Results

Characteristics of the included studies

A total of 806 records were identified via the PubMed search, with eight records from additional sources. After

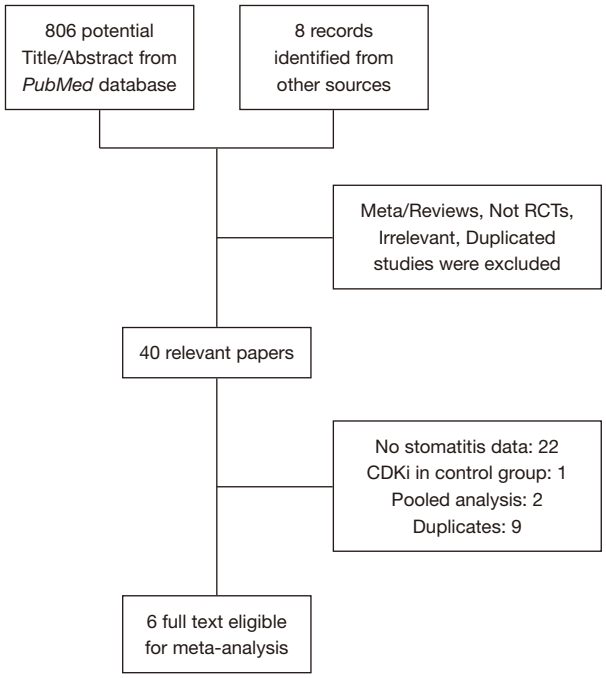

Figure 1 Flowchart of the systematic review process. RCT, randomized controlled trials.

screening the titles and abstracts, 40 papers were eligible for full-text review. Finally, only six RCTs (PALOMA-1, PALOMA-2, PALOMA-3, PALLET, MONARCH-2, and MONALEESA-7) were used for the meta-analysis (2,7,12-15). The filtering process under PRISMA is shown in *Figure 1*.

The basic characteristics of the included studies are displayed in *Table 1*. Two of the six studies used letrozole as the basic ET treatment, three used fulvestrant, and only one used other types of ET. The risk of bias of the studies included in the meta-analysis was evaluated using the Cochrane risk of bias tool and the results are shown in *Table 2*.

Meta-analysis results

A total of 2,980 patients in the safety population were included in the meta-analysis. Of these patients, 1,849 received CDK4/6Is plus ET and 1,131 were in the control group (ET alone). The total number of stomatitis events occurred in 378 (20.4%) patients in the CDK4/6Is arm compared to 105 (9.3%) patients in the control group. The pooled RR for any-grade stomatitis was 2.02 (95% CI: 1.65–2.48), and the absolute RD was 0.10 (95% CI: 0.05–0.15) (*Figure 2* and *Figure 3*). High-grade stomatitis was rare in both groups, while the number in the treatment group (11 patients) was significantly larger than that in the control group (1 patient).

Subgroup analysis was performed because the patients were treated with different CDK4/6Is and ETs. Due to the limited number of studies in some subgroups, there were just three pairs of pooled results, as shown in *Table 3*, including the letrozole ET group, fulvestrant ET group, and palbociclib-containing regimen group. In the letrozole ET group included in the PALOMA-1 and PALLET studies, letrozole was given as basic ET treatment to 461 patients. Stomatitis was observed in 30 patients (10.6%) in the study arm and only two patients (1.1%) in the control arm. The pooled RR in the letrozole group (8.50, 95% CI: 2.22–32.57) was markedly higher than that in the fulvestrant ET group (2.03, 95% CI: 1.62–2.55). However, the pooled RD showed no significant difference between these two groups.

Among the 1,644 patients in the PALOMA-1, PALOMA-2, PALOMA-3, and PALLET studies, 1,073 patients were given palbociclib plus ET (letrozole or fulvestrant), while 571 patients were in the control arm. The incidence of stomatitis in the palbociclib arm was 25.1% (269 patients) versus 9.8% (56 patients) in the control arm. The pooled RR in this subgroup (2.44, 95% CI: 1.88–3.18) was higher than the RR (2.02, 95% CI: 1.65–2.48) from the full study set with limited significance (*Table 3*). Moreover, this RR was higher than the RRs calculated for two studies using ribociclib (1.29, 95% CI: 0.78–2.12) or abemaciclib (1.62, 95% CI: 1.06–2.49) in the treatment arm. This was also observed for the pooled RD estimation, where the RD for patients receiving palbociclib was 0.13 (95% CI: 0.08–0.18). However, the RDs for patients receiving ribociclib and abemaciclib were 0.02 (95% CI: –0.02–0.06) and 0.07 (95% CI: 0.01–0.12), respectively.

Discussion

This study systematically reviewed the risk of stomatitis with CDK4/6Is among breast cancer patients. A total of 20.4% of patients receiving CDK4/6Is had suffered any-grade stomatitis, with RR and RD values of 2.02 (95% CI: 1.65–2.48) and 0.10 (95% CI: 0.05–0.15), respectively. Subgroup analysis revealed that all types of CDK4/6Is had adverse stomatitis reactions, among which, patients receiving palbociclib had the highest risk.

Stomatitis is a common adverse event in breast cancer radiotherapy and chemotherapy, and it is also typical in another targeted treatment, namely, everolimus, one of the

Table 1 Basic characteristics of the studies included in the meta-analysis

Study	Author (year)	Study phase	Study design	Treatment arms	Cancer type	No. of patients	Safety population		No. of stomatitis	
							CDK4/6 inhibitor	Control	CDK4/6 inhibitor (grade >3)	Control
PALOMA-1	Finn (2015)	Phase 2	Open-label, placebo-control	Palbociclib-Letrozole	OR+/HER2–	165	83	77	10 (0)	2
MONALEESA-7	Tripathy (2018)	Phase 3	Double-blind, placebo-control	Ribociclib-Hormone therapy[a]	HR+/HER2–	672	335	337	32 (1)	25
PALOMA-3	Turner (2018)	Phase 3	Double-blind, placebo-control	Palbociclib-Fulvestrant	HR+/HER2–	521	345	172	104 (3)	24
PALOMA-2	Mukai (2019)	Phase 3	Double-blind, placebo-control	Palbociclib-Fulvestrant	ER+/HER2–	666	444	222	135 (4)	30
MONARCH-2	Sledge (2019)	Phase 3	Double-blind, placebo-control	Abemaciclib-Fulvestrant	HR+/ERBB2–	669	441	223	77 (1)	24
PALLET	Johnston (2020)	Phase 2	No placebo	Palbociclib-Letrozole	ER+/HER2–	307	201	100	20 (2)	0

[a], tamoxifen or non-steroidal aromatase inhibitor.

Table 2 Risk of bias summary

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Free of selective reporting (reporting bias)
MONALEESA-7	√	√	√	√	√	√
MONARCH-2	√	√	√	√	√	√
PALLET	√	√	?	√	√	√
PALOMA-1	√	√	×	√	√	√
PALOMA-2	√	√	√	√	√	?
PALOMA-3	√	√	√	√	√	√

√, low risk; ×, high risk; ?, unclear risk.

mammalian targets of rapamycin inhibition (mTOR) (16). Baselga *et al*. (17) found that the most common adverse reaction caused by everolimus was stomatitis (any-grade stomatitis rate: 11.6%), and among these patients, more than 50% had grade 3 or above stomatitis symptoms. Moreover, BOLERO-2 and BALLET also reported that 12.2–52.8% of breast cancer patients receiving everolimus had suffered stomatitis of any grade, and this adverse reaction was also one of the most important reasons for drug discontinuance (18,19). Furthermore, stomatitis caused by everolimus will not only affect patients' normal medication intake but also adversely impact their quality of life (20).

Although the incidence of CDK4/6Is stomatitis is lower than the rates of hematological and gastrointestinal adverse reactions (8,10), it should not be ignored as this rate might even be higher than the incidence of stomatitis caused by everolimus. Unfortunately, since most cases of stomatitis from CDK4/6Is are mild (grade 2 and below), it has long been neglected clinically. However, its impact on patients' quality of life and secondary influence on patients' health cannot be overlooked (21,22).

As a dominant adverse reaction of CDK4/6Is, stomatitis is mainly manifested as a gray oval aphtha-like ulcer with clear boundaries surrounded by reddened tissue (23). Its

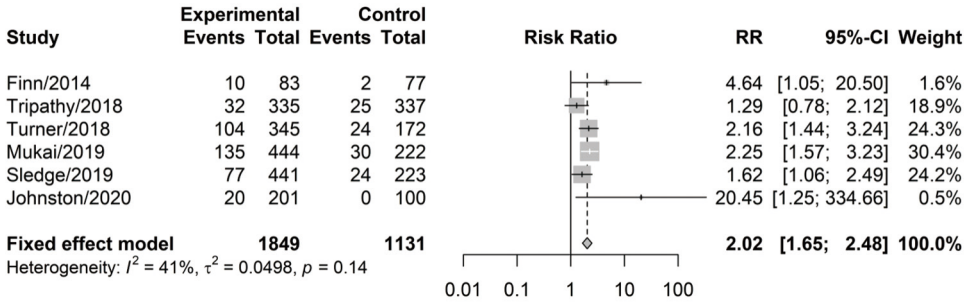

Figure 2 Pooled relative risk for stomatitis in patients with advanced breast cancer receiving CDK4/6 inhibitors vs. controls. CDK4/6, cyclin-dependent kinase 4/6.

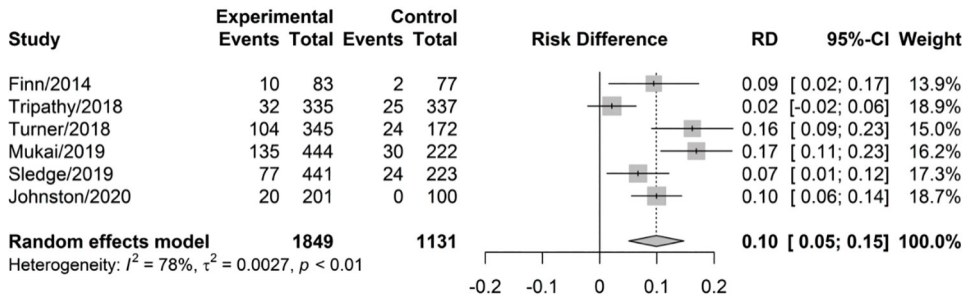

Figure 3 Pooled relative difference for stomatitis in patients with advanced breast cancer receiving CDK4/6 inhibitors vs. controls. CDK4/6, cyclin-dependent kinase

Table 3 Subgroup analysis of pooled RR and RD for patients receiving different CDK4/6 inhibitors and ET

Subgroup[a]	No. of studies	Relative risk		Risk difference	
		Pooled RR (95% CI)	I (%), P value	Pooled RD (95% CI)	I (%), P value
Letrozole ET	2 (461)	8.50 (2.22, 32.57)	2%, 0.31	0.10 (0.06, 0.14)	0%, 0.91
Fulvestrant ET	3 (1,847)	2.03 (1.62, 2.55)	0%, 0.48	0.13 (0.06, 0.20)	73%, 0.02
Palbociclib containing regimen	4 (1,644)	2.44 (1.88, 3.18)	14%, 0.32	0.13 (0.08, 0.18)	55%, 0.08

[a], subgroups containing only one study were not shown in this table. RR, relative risk; RD, risk difference; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy.

impact on patients is not only pain from the wound but also the risk of systemic infection due to destruction of the oral mucosal barrier. Therefore, the occurrence of stomatitis may also increase the risk of other infectious adverse reactions.

According to its severity, stomatitis can be divided into 4 grades: grades 1 and 2 have mild symptoms, and patients can eat but need to modify their diet, while patients with grades 3 and 4 stomatitis cannot eat and drink normally (24). We found that the number of patients with severe stomatitis (grades 3 and 4) in the trial group was significantly higher than that in the control group (11 cases *vs.* one case). The inability to eat would directly affect the quality of life and nutrient intake by the patients. Thus, despite the low proportion of high-grade CDK4/6Is stomatitis, we should pay more attention to CDK4/6Is-related stomatitis because approximately one-fifth of patients will suffer from its secondary influences.

At present, CDK4/6Is plus ET has become the first-line therapy for HR(+)/HER2(–) advanced breast cancer without

visceral risk. For these patients, doctors are often more concerned with survival than with mild adverse reactions. However, due to the impact of stomatitis on patients' quality of life and the secondary adverse reactions it may cause, the clinical management of stomatitis is also critical. For mild stomatitis, there is no need to suspend targeted therapy and local supportive treatment with alcohol-free mouthwash or saline gargles and cold compresses is adequate. In the case of everolimus-related grade 3 or recurrent grade 2 stomatitis, it is recommended to suspend the treatment until it returns to grade 1 or below (24). In this study, we did not observe drug discontinuance of CDK4/6Is due to severe stomatitis even though there were some grade 2 and 3 stomatitis cases. Combined with the management experience of everolimus-related stomatitis, the absence of CDK4/6I discontinuance does not mean that the impacts of stomatitis are unimportant. In contrast, there is still a gap between current clinical measures of CDK4/6Is-related stomatitis and similar classical therapies.

In 2020, two clinical studies of CDK4/6Is for early adjuvant therapy reported at the ESMO conference showed great discrepancies in discontinuation rates, and a high incidence of stomatitis associated with some of these agents may be one reason. According to one report, the discontinuation rate of abemaciclib plus ET in the Monarch E study was 16.6% (25), while another study (named Pallas), which focused on the postoperative treatment effect of palbociclib combined with ET, reported a disappointingly high discontinuation rate (42.2%), resulting in Pallas' failure to reach its primary endpoint (26).

Patients' different responses to adverse events would be the main reason for discontinuation. Compared with the Monarch E study, which recruited high-risk patients with at least one lymph node metastasis, 41.3% of patients in Pallas were medium risk. The survival expectancy of patients with a high metastasis risk is greatly reduced, so their tolerance of adverse reactions is better than that of low- and medium-risk patients. Therefore, adverse reactions such as stomatitis were more likely to cause discontinuance in the Pallas study.

To improve patient compliance in follow-up research and clinical practice, we should strengthen the management of stomatitis in patients with different cancer stages. For instance, we can take interventions before and during treatment, such as dental checkups, regular oral care, and good oral hygiene, to reduce the harm of stomatitis.

We performed the first systematic review and meta-analysis to explore the risk of CDK4/6Is-related stomatitis, and analyzed the sources of risk differences (RDs) as well as their implications for patients' quality of life and drug discontinuance. Due to the lack of individual-level data, some important personal confounding variables, such as age, genetic changes, and previous treatment history, could not be controlled. Secondly, a more thorough comparison of CDK4/6Is combined with ET among different subgroups was unable to be conducted because of the limited number of articles included in the meta-analysis. However, our subgroup analysis still found some meaningful results. Finally, the explanations of the secondary effects of stomatitis in this study were only based on the literature and professional knowledge. The specific quantitative impacts on patient quality of life and compliance require further questionnaire investigation.

Conclusions

In summary, our analysis found that, compared with the control group, all types of CDK4/6Is, especially palbociclib, could increase the risk of stomatitis. Although high-grade stomatitis cases are rare, secondary damage, such as impacts on patient quality of life, risk of infection, and medication compliance, could be severe. Therefore, the prevention and management of stomatitis should not be overlooked. To quantify the relationship between stomatitis and patients' quality of life and health status, more comprehensive individual-level data are needed in future studies.

Acknowledgments

Funding: This study was funded by the Science and Technology Department of Sichuan Province (No.2017SZ0065).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1156

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1156). All authors report funding from Science and Technology Department of Sichuan Province (No .2017SZ0065). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This article does not include any studies with human participants or animals performed by any of the authors.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25-35.
3. Chlebowski RT. Changing concepts of hormone receptor-positive advanced breast cancer therapy. Clin Breast Cancer 2013;13:159-66.
4. Rocca A, Farolfi A, Bravaccini S, et al. Palbociclib (PD 0332991) : targeting the cell cycle machinery in breast cancer. Expert Opin Pharmacother 2014;15:407-20.
5. Im SA, Lu YS, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med 2019;381:307-16.
6. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2015;373:209-19.
7. Tripathy D, Im SA, Colleoni M, 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 2018;19:904-15.
8. Kassem L, Shohdy KS, Lasheen S, et al. Hematological adverse effects in breast cancer patients treated with cyclin-dependent kinase 4 and 6 inhibitors: a systematic review and meta-analysis. Breast Cancer 2018;25:17-27.
9. Thein KZ, Htut TW, Ball S, et al. Venous thromboembolism risk in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with combined CDK 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res Treat 2020;183:479-87.
10. Shohdy KS, Lasheen S, Kassem L, et al. Gastrointestinal adverse effects of cyclin-dependent kinase 4 and 6 inhibitors in breast cancer patients: a systematic review and meta-analysis. Ther Adv Drug Saf 2017;8:337-47.
11. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
12. Mukai H, Shimizu C, Masuda N, et al. Palbociclib in combination with letrozole in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: PALOMA-2 subgroup analysis of Japanese patients. Int J Clin Oncol 2019;24:274-87.
13. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med 2018;379:1926-36.
14. Johnston S, Puhalla S, Wheatley D, et al. Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor-Positive Early Breast Cancer: PALLET Trial. J Clin Oncol 2019;37:178-89.
15. Sledge GW Jr, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol 2020;6:116-24.
16. O'Shaughnessy J, Thaddeus Beck J, Royce M. Everolimus-based combination therapies for HR+, HER2- metastatic breast cancer. Cancer Treat Rev 2018;69:204-14.
17. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-9.
18. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30:870-84.
19. Jerusalem G, Mariani G, Ciruelos EM, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal

aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). Ann Oncol 2016;27:1719-25.
20. Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017;18:654-62.
21. Mols F, Vingerhoets AJ, Coebergh JW, et al. Quality of life among long-term breast cancer survivors: a systematic review. Eur J Cancer 2005;41:2613-9.
22. Lasheen S, Shohdy KS, Kassem L, et al. Fatigue, alopecia and stomatitis among patients with breast cancer receiving cyclin-dependent kinase 4 and 6 inhibitors: a systematic review and meta-analysis. Expert Rev Anticancer Ther 2017;17:851-6.
23. Seiler S, Kosse J, Loibl S, et al. Adverse event management of oral mucositis in patients with breast cancer. Breast Care (Basel) 2014;9:232-7.
24. Aapro M, Andre F, Blackwell K, et al. Adverse event management in patients with advanced cancer receiving oral everolimus: focus on breast cancer. Ann Oncol 2014;25:763-73.
25. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 2020;38:3987-98.
26. Mayer E, Gnant M, DeMichele A, et al. LBA12 PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol 2020;31:S1145.

(English Language Editor: A. Kassem)

Cite this article as: Long Q, Li X, Wu G, Zhang J, Li H. Oral adverse effects of CDK4/6 inhibitors among breast cancer patients: a systematic review and meta-analysis. Ann Palliat Med 2021;10(6):6556-6563. doi: 10.21037/apm-21-1156

