Potential Movement of CDK 4/6 Inhibitor from Cell Cycle Arrest to Immune Activation in Breast Cancer

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Submission: February 13, 2019; Published: February 27, 2019

Abstract

Three different CDK 4/6 inhibitor was approved in a short time during 2016-2017 by FDA to treat hormone receptor-positive (HR+), HER2 negative (-) advances breast cancer patients. Since the beginning of the preclinical study, palbociclib, ribociclib, and abemaciclib were markedly suppressed proliferations of HR+/HER2- cell lines but less effective to HER2+ and metastatic breast cancer with disease progression after endocrine therapy. Palbociclib was being used in combination with fulvestrant [1]. Ribociclib was approved by FDA as the first line therapy to treat HR+ / HER2- advanced or metastatic breast cancer patients combined with letrozole [2]. Recently generation of CDK 4/6 inhibitor, Ribociclib was approved either alone or in combination with fulvestrant for advanced or metastatic HR+/HER2- breast cancer after endocrine therapy failure [3].

Targeting the abnormal cell cycle of the tumor cells is the chief mechanism of CDK 4/6 inhibitor. In the activation of CDK4/6 through cycling D binding, the cyclin D-CDK4/6 complex phosphorylates the retinoblastoma (Rb) tumor suppressor protein. The phosphorylation of Rb protein releases its suppression effect to E2F transcription factor lead to activate the genes target and move the cells from G1 phase to S phase. In the present of CDK 4/6 inhibitor, phosphorylation of Rb protein was inhibited and suppresses E2F. In turn, it keeps the gene targets off [4–6]. Despite the cell cycle arrest mechanism as the main mechanism, there are emerging evidences that this drug has an important role in tumor microenvironment regulations in breast cancer cells [5].

Tumor microenvironment consists of non-cellular and cellular components such as immune cells. Only targeting the cancer cells and ignoring the tumor microenvironment to eradicate the tumor is not enough since the relationship between both are support each other. Clinically, the tumor microenvironment such as infiltration of immune cells in the tumor site shows significant prognostic value of breast cancer patients. Tumor-infiltrating leucocyte studied most extensively in breast cancer. The TILs consist of T-cell, B-cell, monocyte, NK-cell, and cytotoxic T cell [7]. High TILs concentration in the Luminal-HER2 negative, HER2 positive and triple negative breast cancer (TNBC) subtypes of patients significantly associated with high pathologic complete responses (pCR) after neoadjuvant

Introduction

Rapid advance movement of CDK 4/6 inhibitor from preclinical to the clinical trial becomes a new hope for advances (metastatic) breast cancer. The first CDK 4/6 inhibitor is palbociclib that approved for HR+/HER2- advanced or metastatic breast cancer with disease progression after endocrine therapy. Palbociclib was being used in combination with fulvestrant [1]. Ribociclib was approved by FDA as the first line therapy to treat HR+/HER2- advanced or metastatic breast cancer patients combined with letrozole [2]. Recently generation of CDK 4/6 inhibitor, Ribociclib was approved either alone or in combination with fulvestrant for advanced or metastatic HR+/HER2- breast cancer after endocrine therapy failure [3].

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chemotherapy. Increases the TILs associated with longer overall survival of TNBC. By contrast, increasing in TILs has no association to overall survival in luminal-HER2 negative subtypes [8]. This results in HER2 positive and luminal subtypes maybe caused by the existence of lymphocytes that suppresses the immune system and promotes tumor progression such as T-regulator cell, and myeloid-derived suppressor cell [9]. After success in melanoma and lung cancer patients, immunotherapy rapidly grows to treat the other solid cancer patients including breast cancer. After a low response of breast cancer patients to immunotherapy, recently good news came from TNBC patients' study. Treatment atezolizumab to advanced TNBC with positive PD-L1 expression improve prolong free survival time compared to patients only got chemotherapy as standard treatment. In the middle of this good achievement still left a big question for the PD-L1 negative metastatic breast cancer patients (approximately 59.1%) [10].

Despite inducing G1 cell cycle arrest, growing evidences show CDK 4/6 inhibitor impressive effect on immune activation against breast cancer. Using breast cancer clinical samples, breast cancer cell line, and MMTV-rtTA/tetO-Her2 mice model, treatment abemaciclib inhibit tumor cell proliferation as well as activate the immune cells. First, this drug treatment induces dsRNA through increasing retroviral element endogenous expression. Next turn, it stimulates type I interferons and induces increasing tumor antigen presentation. In the other hand, these drugs also suppress the regulatory T cells proliferation but not the CD8+ or conventional CD4+ T cells. Further, both mechanisms enhance cytotoxic T cell eliminate the breast tumor cells [11]. Interestingly, in prostate cancer, Cyclin D-CDK4 axis regulates PDL-1 expression level through Cullin 3STOP E3 ligase (Cul3STOP). Cyclin D-CDK4 inhibition suppresses SPOP phosphorylation led to SPOP degradation by APC/Ccdh1. This turn decreases PD-L1 ubiquitination and stabilizes its expression on the tumor cells. CDK 4/6 inhibitor treatment alone improve the survival rate compared to the control group in mouse tumor model. Moreover, combination CDK 4/6 inhibitor with anti-PD-1 immunotherapy significantly improve the survival rates compare to both drug-treated in alone [12]. Consistently, in the MMTV-rtTA/tetO-HER2 tumor mice showed similar results. Combination CDK 4/6 inhibitor (abemaciclib) and anti-PD1therapy reduced tumor volume up to 70% at 13 days after initial treatment and stop growing at day 35 [11]. These findings open new hope to improve breast cancer patients get benefit from immunotherapy through CDK 4/6 combination. This combination gives more chance for negative PD-L1 breast cancer patient to response the anti-PD-L1 immunotherapy.

At the beginning of CDK4/6 treatment on triple negative breast cancer subtypes, this drug showed little effect on suppressing cell proliferation. Recently, there growing evidences of chance using this drug to TNBC. In 2016, treated triple-negative breast cancer patient-derived xenograft mice with CDK 4/6 inhibitor could suppress the metastases process. Markedly, palbociclib significantly decreased distant metastases rates to liver (12.5% vs 75%), and lung (25% vs 75%) compared to control group (saline). This study also revealed the mechanism of metastases suppression happen through epithelial-mesenchymal transition. CDK 4/6 inhibition suppresses DUB3 activation lead to destabilizing a key factor promoting EMT, SNAIL1 [13]. In another study, EMT in triple negative breast cancer has an important role in immune cell infiltration to the tumor sites and its activation. Tumors that arise from mesenchymal breast cancer cell lines show immune suppressive phenotype than tumor arising from epithelial cell lines. In mouse model injected with PyMT-Snail high cell lines arising tumors that have more regulatory T cells, M2 macrophages, PD-L1, and low level of MHC-I as well as low activated CD8+ T cells [14]. Moreover, a combination between CDK 4/6 inhibitor and PI3Kα in syngeneic TNBC mouse model significantly increased cytotoxicity and activation of T cells in the tumor sites as well as suppressed the myeloid-derived suppressor cells populations [15].

Conclusion

In the success of immunotherapy against several solid tumors such as melanoma and lung cancer, there is a new hope of breast cancer patients get benefit through the same approach. However, the successful rate still remains low. Here we shortly provide evidences of CDK 4/6 inhibitor effect to immune cells in HER2 and triple negative breast cancer subtypes. By understanding the CDK 4/6 mechanism on immune cell activation, we hope there is a chance to increase the number of breast cancer subtypes get benefit from these drugs. Later by combinations therapy, CDK 4/6 inhibitor could improve the response of breast cancer patients to current immunotherapy in the future.

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How to cite this article: Pamungkas Bagus Satriyo. Potential Movement of CDK 4/6 Inhibitor from Cell Cycle Arrest to Immune Activation in Breast Cancer. Canc Therapy & Oncol Int J. 2019; 13(1): 555855. DOI: 10.19080/CTOIJ.2019.13.555855