

CDK inhibitors in hormone receptor positive advanced breast cancer

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ABSTRACT

Endocrine treatment is the current first line treatment in ER+ advanced breast cancer with a requirement of predictive biomarkers to the treatment and different approaches for endocrine resistance risk. Cyclin dependent kinases (CDKs) are regulating each step of cellular division in mammalian cell cycle and are hyperactivated in cancer cells causing cancer progression. Next generation pan-CDK inhibitors are in clinical development, while clinical trials in breast cancer, particularly in ER+ subtype where the greatest growth inhibition has been observed. Here I will review the data from this new class of drugs.

Keywords: CDK inhibitors, Hormone positive advanced breast cancer, Targeted therapies, Palbociclib, Endocrine therapy resistance

Introduction

Hormone receptor positive (HR+) breast cancer is the most commonly diagnosed molecular subset of advanced breast cancer and benefits highly from endocrine treatment in both adjuvant and metastatic setting with a relatively low toxicity profile [1]. Despite having an indolent course it remains incurable. The current goals of therapy in metastatic breast cancer are maintaining a good quality of life, prolonging the survival and delaying initiation of chemotherapy [2].

Several types of single-agent or combined endocrine treatment modalities are available achieving most of these goals and represent the standard of care for the first line therapy [3]. Nevertheless de novo or acquired resistance develops ultimately with each endocrine regimen. At that point, the patients are usually prone to receive chemotherapy that has little effectiveness and a significant toxicity in this subset of patients.

Unfortunately, lack of predictive biomarkers identifying subgroups of patients that will benefit from endocrine therapy at most is still the current problem addressing future options with combined therapies including the new biological agents. Targeting critical pathways to improve the efficacy of endocrine treatment are in development. The cyclin dependent kinases (CDKs) are a large family of serine threonine kinases interacting with cyclins have a key role in maintaining the control of progression through cell cycle. Since the dysregulation of the cell cycle is a hallmark of unrestricted growth in cancer with a high metastatic potential [4], novel agents targeting CDK pathway has been an attractive option for new treatment modalities [5].

The biology of CDKs in cancer

The CDKs are regulating the each step of cellular division in mammalian cell cycle and are hyperactivated in cancer cells causing cancer progression. There are 2 groups of CDKs based on their activity in cell-cycle progression or transcription. Most of the human cells have diploid DNA content exiting the cell cycle and are maintained in a quiescent G0 state. Extracellular signals including activation by peptide growth factors (such as RAS, MAPK and mTOR) and nuclear receptors (such as estrogen receptor), drive the cell cycle into G1 phase and then S phase from quiescent G0

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phase [6-9]. This occurs mainly by association with D-type cyclins (Cyclin D1, cyclin D2 and cyclin D3) through the regulation of CDK4 or CDK6 complex that are structurally related, similar proteins [10-12]. Cyclin D1 is the best characterized D-type cyclin that is expressed to promote the activity of CDK4 and CDK6 [13].

In contrast to other CDKs, cyclin association is controlled by multiple mechanisms in CDK4 and CDK6. Overexpression/induction of INK4 proteins including p16, p15, p18 and p19 function as inhibitors of CDK4 and CDK6 in response to stress conditions causing G1 arrest of the cell cycle [7, 14, 15]. Similar to other CDKs, CDK4 and CDK6 are subjected to phosphoregulation with a unique preference to the phosphorylation of the tumor suppressor retinoblastoma protein (RB) and the related proteins (RBL1 and RBL2) [16, 17]. RB functions as a multiprotein complex in cell cycle by binding to E2F transcription factors and suppressing transcription of the genes that are regulated by E2Fs. Thus, the phosphorylation of RB by CDK4 and CDK6 causes the release of E2F initiating the progression of cell cycle [18, 19].

Deregulation of cyclin D1, RB, INK4 proteins as well as CDK4 and CDK6 can occur in various types of cancers. Importantly, distinct mechanisms of CDK4/6-RB-p16 pathway dysregulation is mutually exclusive and are frequently tumor-type specific [20]. Cancer Genome Atlas demonstrated the aberrations causing hyperactivation of cyclin D1-CDK4/6 in particularly ER+ breast cancers [21]. Furthermore, cyclin D1 has been shown to activate ER in the absence of estrogen playing a role in endocrine resistance [22]. In addition, alterations in p16, increase in RB phosphorylation may be associated with resistance to endocrine treatment in breast cancer patients providing a strong rationale for targeting of the pathway [23-26].

Targeted inhibition of CDK4 and CDK6

CDK inhibitors have two main classes based on their target range: 1. Broad range CDK inhibitors act on a variety of CDKs including CDK4/CDK6; 2. Cell –cycle specific inhibitors act on CDK4/CDK6. CDKs mainly block the ATP binding pocket. Early efforts to target CDKs initially started with pan-CDK inhibitors causing a notable toxicity although activity has been observed in hematological/solid malignancies with a lack of appropriate patient selection [27]. Next generation pan-CDK inhibitors are in clinical development, while clinical trials in breast cancer, particularly in ER+ subtype where the greatest growth inhibition has been observed, are focused on inhibiting cyclinD1-CDK4/6 interaction. Elevated RB and cyclin

D1 or decreased p16 seem to be promising predictors of response in these clinical trials while lack of RB function (loss/inactivation) can cause resistance to CDK4/6 inhibitors since the inhibition depends on downstream of RB in several cancer types [20, 28, 29].

Endocrine therapy in combination with CDK inhibitors

Resistance to existing endocrine therapies remains a major challenge with recent advances in clarifying molecular mechanisms in disease progression including cross-talk between estrogen receptor (ER) and various growth factor receptor and/or intracellular signaling pathway. Therefore, to improve the efficacy of endocrine treatment by combining targeted agents with endocrine therapy is currently being evaluated with numerous agents including mTOR, PI3K, Akt, cyclin-dependent kinase 4/6, SRC and histone deacetylase inhibitors [30, 31]. Preclinical data suggests that targeting mTOR or cyclin-dependent kinase 4/6 (CDK4/6) pathway might increase the endocrine sensitivity [32, 33] carrying over these drugs to clinical trials.

Addition of everolimus, an mTOR inhibitor, to endocrine therapy (exemestane) significantly improved progression-free survival (PFS) of HR+ advanced breast cancers in BOLERO-2 trial (6.9 vs. 2.8 months, hazard ratio 0.43, 95% CI 0.35–0.54; $p < 0.001$) [34] while combination of another mTOR inhibitor, temsirolimus, and endocrine therapy did not improve PFS in HORIZON study [30, 35, 36]. Although it seems to be unclear whether addition of mTOR inhibitors should be combined with endocrine therapy to restore endocrine treatment sensitivity, everolimus is approved for aromatase inhibitor (AI) resistant advanced disease based on BOLERO-2 trial [34, 35, 37, 38]. Several PI3K inhibitors are in clinical development with a recent non-significant improvement in PFS in HR+ AI resistant metastatic breast cancer [39, 40]. Three oral agents selectively targeting CDK4/6 developed recently are palbociclib, abemaciclib and LEE011 [1, 36] and are currently under clinical development:

1. Palbociclib

The Phase II, randomized PALOMA-1/TRIO-18 trial was designed to evaluate safety and efficacy of palbociclib in combination with letrozole and letrozole alone in HR+ HER2 negative advanced breast cancer. Patients entered in two cohorts, cohort 1 (N=66) was unselected for potential biomarkers, cohort 2 (N=99) selected for tumor cyclin D amplification and/or loss of p16. The study has shown a

significantly improved PFS in the combination arm (20.2 vs. 10.2 months; HR, 0.488; 95% CI, 0.319–0.748; one-sided $P = 0.0004$) giving rise to the approval of the drug by FDA in US recently [35, 41]. Evaluation of cohorts 1 and 2 found improvements in both groups with the addition of palbociclib, but no apparent correlation between presence of biomarker and improved outcomes (cohort 1, PFS 5.7 vs 26.1 month, HR 0.299, $p < 0.0001$; cohort 2 PFS 11.1 vs 18.1 month, HR 0.508, $p = 0.0045$). No improvement in overall survival was observed in this small population (OS 33.3 months letrozole vs 37.5 months letrozole and palbociclib, HR 0.813, $p = 0.2105$). Side effects were mainly hematological, with grade 3/4 neutropenia and leucopenia reported in 54% and 19% of patients receiving palbociclib, respectively. The cumulative incidence of neutropenia remained stable (75.8 %) after 2 years follow-up, suggesting the hematologic toxicity occurs early in treatment and no data support long-term or cumulative hematologic toxicity after the exposure [35]. Phase III development is underway worldwide investigating its use as first-line treatment in advanced breast cancer, as well as treatment of recurrent advanced breast cancer and high-risk (PALOMA-2, PALOMA-3, PEARL studies), early-stage breast cancer (PENELOPE-B, DFHCC 13-559 studies) [1, 41].

2. Abemaciclib

Preclinical data for abemaciclib have shown activity as both monotherapy and in combination with chemotherapy, as well as possible passage across the blood-brain barrier compared to palbociclib [42, 43]. But, no biomarkers except hormone positivity were predictive of response, including evaluation of cyclin D1 and Rb in Phase I trials. Phase II/III studies offer aromatase inhibitor with or without abemaciclib in the firstline setting, and post progression on endocrine therapy. A phase II study, MONARCH, is evaluating abemaciclib monotherapy in post-progression on chemotherapy in the metastatic setting [1].

3. LEE011

Hematologic and GI toxicity with LEE011 appear to be less than the other two agents in phase I trials [44]. Phase III trial MONALEESA-2 randomized patients to letrozole with or without LEE011 in the first-line setting of metastatic HR+/HER2-disease. In the preoperative setting, MONALEESA-1 is evaluating the contribution of LEE011 to neoadjuvant aromatase inhibitor. A randomized phase Ib/II study of LEE011 with the PI3K inhibitor BYL719 and letrozole (NCT01872260), and a randomized phase Ib/II study of LEE011 with the mTOR inhibitor everolimus and

exemestane (NCT01857193) in pretreated metastatic HR+ breast cancer are ongoing.

Conclusions and future directions

Endocrine treatment is the current first line treatment in ER+ advanced breast cancer with a requirement of predictive biomarkers to the treatment and different approaches for endocrine resistance risk. Accumulating preclinical data have shown that inhibition of CDK4/6 pathway has an impact on decreasing breast cancer progression through the loss of cell cycle control. Since the early clinical data have suggested the benefit of CDK4/6 inhibition as monotherapy and combined therapy with endocrine treatment modalities in ER+ breast cancer, predictive biomarker aside from estrogen receptor for CDK4/6 inhibition needs to be identified including amplification or overexpression of cyclin D and/or RB. Studies investigating both poly-endocrine treatment and new agents in combination with endocrine treatment are ongoing and needs a careful consideration against additional toxicity and cost. Hematological and gastrointestinal toxicities seems to be common, but manageable supporting their use in the clinic safely. In addition, investigation of primary and secondary resistance mechanism of the drug will be important for the selection of best population who may benefit from these drugs and further treatment modalities or drug development strategies. Depending on the fact that CDK4/6 inhibitors may be an option for patients who are resistant to endocrine treatment, substantial efforts in clinical trials are ongoing in both advanced and early stage breast cancer treatment.

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