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Palbociclib: A breakthrough in breast carcinoma in women

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ABSTRACT

Breast cancer (BC) is the most common cancer and leading cause of death in women worldwide. Cellular proliferation, growth, and division are tightly controlled by the cell-cycle regulatory machinery. An important pathway is cyclin-dependent kinases (CDKs) which regulate cell cycle and thus control transcriptional processes. In human cancer, multiple CDK family members are commonly deregulated. The cyclin D-CDK4/6-retinoblastoma (RB) protein-INK4 axis is particularly affected in many solid tumors which leads to cancer cell proliferation. This has led to long-standing interest in targeting CDK4/6 as an anticancer strategy. Different investigational agents that have been tested which inhibit multiple cell cycle and transcriptional CDKs but have carried excessive toxicity thus failed to stand the rational of human use. Amongst several selective and potent inhibitors of CDK4/6, palbociclib is the first to be accessed suitable for human use having explicit selectivity toward CDK4/6. Its mechanism is to arrest cells in G1 phase by blocking RB phosphorylation at CDK4/6-specific sites without affecting the growth of cells which are RB-deficient. Studies conducted in patients of BC having cells with advanced RB-expression demonstrated acceptable side effects but dose-limiting toxicities primarily neutropenia and thrombocytopenia, with prolonged stable disease in patients.

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Introduction

Cancer is a group of diseases characterized by the uncontrolled cell division and metastasis of abnormal cells. In women, second most common cancer is breast cancer with a very high metastatic probability, and thus morbidity and mortality. The

National Cancer Institute in the United States estimates close to 232,670 women who were diagnosed having breast cancer; out of which 40,000 succumbed to the disease in 2014.¹ Cell-cycle transition and its progression to cell division are coordinated by cyclin-dependent protein kinases (CDKs).² Aberrancy in cell cycle control is ubiquitous in cancer manifestation among many known pathways, which get

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disarrayed.^{3,7,8} One of most important pathways is CDK4/6, which is over-activated in numerous cancers, resulting in loss of proliferative control in cell division.⁴⁻⁶ In view of high morbidity and mortality in breast carcinoma, the US FDA granted an accelerated approval to palbociclib, a unique drug of its class, on 3 February 2015 based on findings from the phase II PALOMA-1 trial. In this open-label phase II study, treatment with this novel CDK4/6-inhibitor palbociclib plus letrozole substantially reduced the risk of disease progression by 51% in comparison to letrozole alone.

Structure

The chemical name of palbociclib is 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one. It is a molecule with a 2-aminopyridyl substitution at the C2-position of a pyrido(2,3-*d*)pyrimidin-7-one structure of the drug. The molecular formula for palbociclib is C₂₄H₂₉N₇O₂. The molecular weight is 447.54 Da, and its structural formula is shown in Fig. 1.

Cell cycle

Physiologically, cell division and subsequently the cell cycle are intricately regulated by physiological regulator molecules like cyclin. Pro-mitogenic signals upregulate and activate cyclin D, resulting in the complexing of cyclin D with

CDK4/6.³ These complexes facilitate phosphorylation of retinoblastoma (RB) leading to the release of bound E2F transcription factors facilitating cells to divide.⁹ Positive regulators of the cell cycle are the CDKs and their cyclin partners, while RB and other tumor suppressors (p16^{INK4a}, p15^{INK4b}, and p18^{INK4c}), and the CDK-interacting protein/kinase inhibitory protein (Cip/Kip) family negatively regulate the cell cycle (Fig. 2).¹⁰

Mechanism of action: cell-cycle control in breast cancer

Transition from G1 to the S phase is controlled by the retinoblastoma tumor suppressor gene product (RB).⁹ RB is a critical negative regulator of the cell cycle, preventing premature cell division by complexing with the E2F transcription factors, thereby inhibiting G1/S transition.^{12,13} Loss of RB expression occurs in 20–35% of breast cancers; thus, the majority of breast cancers maintain intact or functioning RB. The incidence of RB loss is dependent on the clinical subtype of breast cancer and is more common in triple-negative breast cancer (TNBC) compared with other subtypes. RB inactivation facilitates tumor progression through loss of proliferation control and conversion to an invasive phenotype.^{11,12} In general, it is associated with poorer differentiation and increased metastatic potential. In the absence of functional RB, cell-cell adhesion is disrupted, and epithelial-to-mesenchymal transition is facilitated, potentially underlying the increase in metastases observed. However, the impact of RB loss is dependent on the breast cancer subtype.¹⁴ RB dysregulation is associated with poor prognosis in estrogen receptor (ER)-positive breast cancer but better outcomes in ER-negative tumors.^{15,16} This difference in outcomes may be driven by differing responses to therapy, as RB loss increases sensitivity to DNA-damaging agents but results in continued proliferation in tamoxifen-treated xenografts.¹⁵ CDK4 and/or CDK6 are essential most proteins responsible for regulation of cell division.¹³ Cyclin D is primarily overexpressed and/or amplified in large number of tumors. Palbociclib is a novel, orally administered, a cell cycle specific drug which acts by inhibiting molecules, known as CDKs 4/6. Inhibition of CDK4/6 prevents DNA replication by arresting progression from G1 to S phase during cell division.^{17,20} Interruption of this mechanism prevents tumor cell proliferation through control of the cell cycle.

Primary indication

US FDA has granted accelerated approval on 3 February 2015 to the drug for use in postmenopausal women with ER-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who as yet not have received an endocrine-based therapy. Palbociclib is approved for use in combination with letrozole, an aromatase inhibitor used to treat certain kinds of breast cancer in postmenopausal women. The drug has proved a significant improvement in safety and effectiveness in the treatment of a serious condition of metastatic breast cancer as well as meets an unmet medical need till now. The average overall survival (OS) was increased to 37.5 months with palbociclib.^{18,19}

Fig. 1 – Palbociclib, CDK4/6 inhibitor.

Fig. 2 – The cell division and regulators. Notes: Cell division and cell cycling are a highly regulated process by many positive and negative controls. Signals mitogenic in nature upregulate and in the process activate cyclin D which results in the interaction of cyclin D with CDK4 or 6. Complexes so formed facilitate the phosphorylation of RB resulting in release of bound E2F transcription factors and facilitating the cell division. The positive regulators of the cell cycle are CDKs and many cyclin partners, while RB are the tumor suppressors (p15^{INK4b}, p16^{INK4a}, p19^{INK4d} and p18^{INK4c}), besides the CDK-interacting protein/kinase inhibitory protein (Cip/Kip) family negatively regulate the cell cycling process. Abbreviations: NF-κB, nuclear factor κB; AR, androgen receptor; PR, progesterone receptor; ER, estrogen receptor; RB, retinoblastoma; CDK, cyclin-dependent kinase; P, phosphate; R, restriction point.

Source: Adapted from K.A. Cadoo et al.²

Recommended dosage

The recommended dose is 125 mg/day for 21 days, followed by next 7 days without treatment in 28-day cycles along with the caution of periodic monitoring of complete blood count starting prior to start of therapy and at the beginning of each cycle, and on day 14 of the first two cycles, besides consider

repeating the complete blood count monitoring 1-week later or as clinically indicated. The drug is advised preferably be taken with food and in combination with letrozole 2.5 mg once daily continuously approximately the same time each day (Table 1).

Pharmacokinetics parameters

The drug is administered orally which is absorbed slowly from intestine in 6–12 h, with a median T_{max} of about 5.5 h, has a large volume of distribution and thus distributes widely in the peripheral tissues, and is slowly eliminated with a half-life of 26 h and thus also cumulates on repeated dosing. The mean absolute bioavailability after an oral 125 mg dose is 46%. Steady plasma levels are achieved within 8 days following repeated once a day dosing. It also shows low to moderate variability with dose-dependent increase in plasma concentration. Food intake reduces inter-subject variability of palbociclib, which supports administration with food. Palbociclib binding to human plasma proteins in vitro approximates 85%, with no concentration dependence over the concentration range of 500–5000 ng/mL. The mean apparent volume of distribution is 2583 L. It undergoes hepatic metabolism by CYP3A hepatic enzyme in humans; the primary metabolic pathways involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. It

Table 1 – Multiple-dose parameters on day 21 for the palbociclib of 125 mg once daily.

Parameter	Palbociclib (125 mg)
T_{max} (h)	5.5 (2.0–9.8)
C_{max} (ng/mL)	97.4 (41)
C_{trough} (ng/mL)	47.0 (48)
AUC_{0-24} (ng h/mL)	1733 (42)
$t_{1/2}$ (h)	25.9 (29)
CL/F (L/h)	80.6 (34)
Vz/F (L)	2793 (15)
Rac	2.2 (1.5–2.9)

Note: Data are median (range) for T_{max} and Rac, arithmetic mean (% CV) for AUC_{0-24} , CL/F, C_{max} , C_{trough} , and Vz/F. Abbreviations: CL/F, apparent oral clearance; Vz/F, apparent oral volume of distribution during the terminal elimination phase following oral administration.

undergoes extensive metabolism with unchanged drug accounting for 2.3% in feces and 6.9% in urine. The major route of excretion of drug is in feces (74.1% of dose), with 17.5% in urine as metabolites. The mean ($\pm$ standard deviation) plasma elimination half-life was 29 ($\pm$ 5) h in patients with solid organ tumors.

Adverse effects

In PALOMA-1 trial the most common side effects of the drug is grade 3/4 neutropenia which is remarkably higher in the palbociclib arm in comparison to letrozole alone (54% vs 1%), higher rate of grade 3/4 leucopenia (19%), pulmonary embolism (5%), fatigue (4%), diarrhea (2%), anemia, respiratory infection, nausea and vomiting, stomatitis, alopecia, thrombocytopenia, anorexia, asthenia, peripheral neuropathy and epistaxis. However, no reported case of febrile neutropenia or neutropenia-related infections was observed however caution is advised while use of the drug. The most frequently reported serious adverse events which let the discontinuation of palbociclib in the combination were pulmonary embolism (4%) and diarrhea (2%). Also, a decrease in hemoglobin (83% vs 40%), leukocytes (95% vs 26%), lymphocytes (81% vs 35%), and platelets (61% vs 16%) was observed at higher rate in patients treated with palbociclib plus letrozole vs letrozole alone.

Pregnancy and lactation

Palbociclib is a type C category drug as adequate information in pregnant women is not available. It is advised to use appropriate contraception during therapy and for at least 2 weeks after the last dose. It is advisable for female to contact healthcare provider, if one conceives or if pregnancy is suspected during treatment. It is advisable to withhold breastfeeding while on therapy as potential for serious adverse reactions in nursing infants is there being drug secreted in breast milk.

Pediatric population

Pharmacokinetics of drug is not known in patients <18 years of age.

Drug interactions

Strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole) to be avoided or reduce the dose to 75 mg/day. Grapefruit or grapefruit juice may disproportionately increase plasma concentrations and preferably be avoided. CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and St John's Wort) also be avoided as the plasma concentration and half-life of drug may become suboptimal. Letrozole has no drug interaction with palbociclib, when the two drugs are coadministered.

Effect of palbociclib on transporters

In vitro evaluations indicate that palbociclib has a minimal potential to inhibit the activities of wide varieties of drug transporters – breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1, OATP1B3 at therapeutic relevant concentrations.

Effect of transporters on palbociclib

Data in in vitro studies suggest that BCRP mediated transport and P-gp are unlikely to affect the extent of oral absorption of palbociclib at therapeutic doses.

Hepatic and renal impairment

The drug has not been studied in subjects with hepatic impairment or in patients with severe renal impairment (CrCl <30 mL/min).

Drugs that may have their plasma concentrations altered by palbociclib

Palbociclib is a weak time-dependent inhibitor of CYP3A. Midazolam co-administration with repeated doses of palbociclib is likely to increase the midazolam plasma concentration by 61%, in healthy subjects, as compared to only midazolam administration. The dose of drugs with a narrow therapeutic index and being themselves sensitive to CYP3A as substrate (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) may need to be reduced and carefully monitored on co-administration with palbociclib as their plasma levels may increase.

Future possibilities

With this drug palbociclib, there are a number of planned phase III clinical trials to explore treatment for patients with advanced breast cancer. The PALOMA-3 trial is to compare palbociclib and fulvestrant against fulvestrant alone in women with HR-positive, HER2-negative metastatic breast cancer following progression on prior therapy with endocrine (NCT01942135). The phase III PENELOPE-B trial is to access post-neoadjuvant treatment with palbociclib and therapy with endocrinal agent in HR-positive patients having residual disease following chemotherapy and surgery (NCT01864746).²⁰ Besides, for patients with HR-positive metastatic breast cancer that are resistant to treatment with aromatase inhibitors, an open-label phase III PEARL trial is to compare combination of exemestane and palbociclib with capecitabine in a 1:1 ratio (NCT02028507). Other tumors in phase 1 trial includes kidney, melanoma, liposarcoma, appendiceal, thymoma, peritoneal, ovarian, and testicular.

Arrays of CDK inhibitors, with diversified modes of actions designed to target the cell cycle arrest at the G1–S checkpoint

are currently in various phases of clinical development. To name a few are flavopiridol (CDK1, 2, 4, and 7 inhibitor),²¹ SCH 727965 (CDK1, 2, 5, and 9 inhibitor),²² SNS-032 (formerly BMS-387032; CDK2, 7, and 9 inhibitor),^{22,21,23–27} AT7519M (CDK1, 2, 4, and 5 inhibitor),²⁴ PHA 848125 (inhibitor of CDKs 1 and 2 in addition to neurotrophic tyrosine kinase receptor type 1, TRKA),²³ and indisulam (E7070, which blocks cells in G1 phase and reduces expression of cyclins A, B1, and CDK2).^{25–27}

Conclusion

A cell-cycle regulatory mechanism is critical to cell division and maturation physiologically. The unpredicted dysregulation of this mechanism is a critical step in the development of cancerous cells contributing to tumor growth. RB, being an inhibitory control to CDK4/6, inhibits the cell division and growth by suppressing DNA replication. Anti-cancer agent palbociclib is an unique leading molecule acting through inhibition of CDK4/6 particularly in breast cancer models in animal studies. Since its activity surmounts to action through inhibition of CDK4/6, it has no action in RB deficient animal models. It has also been found that palbociclib is effective in tamoxifen-resistant breast cancer lines too. It also has been having synergistic effect with tamoxifen and trastuzumab in ER-positive and HER2-positive cell lines, respectively. Most prominent toxicity as observed with use of palbociclib is dose dependent neutropenia, which is also its dose-limiting toxicity. Further in phase II studies, the efficacy of drug in breast cancer was established; however, its combination with letrozole was even more efficacious and provides striking improvement in PFS. Furthermore, various clinical studies are rigorously exploring the combination of the drug with letrozole and many newer entities through CDKs including LEE001 and LY2835210 in breast cancers. These newer drugs are really exciting and not far in development as palbociclib. Besides, palbociclib and selective ER modifiers offer a great promise in ER-positive breast cancers too.

Conflicts of interest

The authors have none to declare.

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