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Palbociclib

Updated: February 1, 2016.

OVERVIEW

Introduction

Palbociclib is a unique cyclin-dependent kinase inhibitor that is used in combination with aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Palbociclib is associated with transient and usually mild elevations in serum aminotransferase during therapy, but has yet to be linked to cases of clinically apparent acute liver injury.

Background

Palbociclib (pal" boe sye' klib) is an orally available, specific inhibitor of cyclin-dependent kinases that is used in combination with aromatase inhibitors in the therapy of postmenopausal women with metastatic breast cancer that is positive for the estrogen receptor (ER+), but negative for human epidermal growth factor receptor 2 (HER2-). The cyclin kinases 4 and 6 regulate the cellular transition from the G1 to the S phase of the cell cycle. Inhibition of this transition blocks the progression of the cell cycle and results in growth arrest in rapidly dividing cells. The addition of palbociclib to letrozole or fulvestrant (aromatase inhibitors) therapy of metastatic breast cancer (ER+, HER2-) in postmenopausal women was associated with a prolongation of disease free survival. Palbociclib received accelerated approval for use in the United States in 2015, and it is still under close evaluation for its long term safety and efficacy. Palbociclib is available in capsules of 75, 100 and 125 mg and the typical maintenance dose is 125 mg once daily in 21 day cycles every 28 days indefinitely or until there is disease progression. Common side effects include fatigue, nausea, diarrhea, anorexia, neutropenia, fever, anemia, thrombocytopenia, epistasis, peripheral neuropathy and pulmonary embolism. Severe adverse events include neutropenia fever and sepsis.

Hepatotoxicity

In the large clinical trials, adverse events were common and led to dose reductions in one-third of patients and discontinuation in 8%. Publications on the efficacy and safety of palbociclib have not mentioned serum ALT elevations or hepatotoxicity. There have been no publications or case reports of clinically apparent liver injury attributable to palbociclib; however, there has been only limited, general clinical use of this kinase inhibitor and serum enzyme elevations can occur during treatment.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury and limited general availability).

Mechanism of Injury

The possible causes of serum enzyme elevations or liver injury from palbociclib therapy are not known. Palbociclib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury might be caused by production of a toxic or immunogenic intermediate. Because it is a substrate for CYP 3A4, palbociclib is susceptible to drug-drug interactions with agents that inhibit or induce this specific hepatic microsomal activity.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) or any elevations accompanied by jaundice or symptoms should lead to dose reduction or temporary cessation. There is no evidence to suggest a cross reactivity in risk for adverse events, hypersensitivity or hepatic injury between palbociclib and other protein kinase inhibitors.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Other Cyclin-Dependent Kinase Inhibitor Drugs: Ribociclib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Palbociclib – Ibrance®

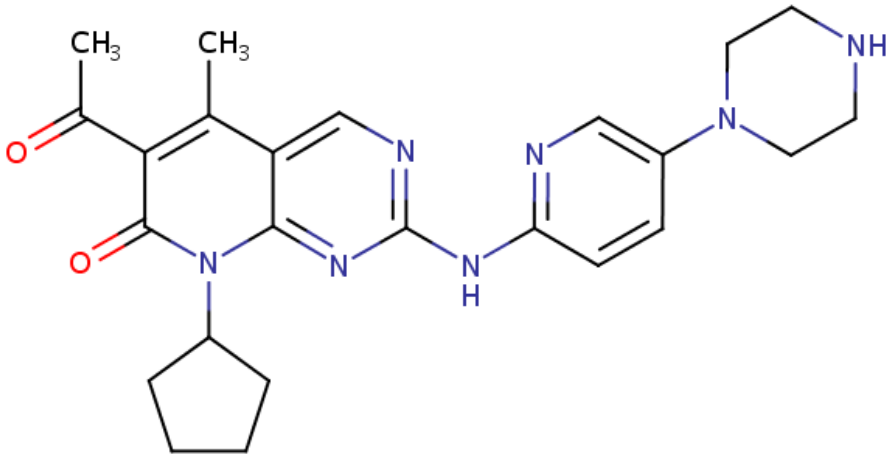
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Palbociclib	571190-30-2	C24-H29-N7-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 01 February 2016

Zimmerman HJ. Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of tyrosine kinase inhibitors such as palbociclib).

DeLeve LD. Erlotinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several tyrosine kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not palbociclib).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Spraggs CF, Xu CF, Hunt CM. Genetic characterization to improve interpretation and clinical management of hepatotoxicity caused by tyrosine kinase inhibitors. Pharmacogenomics 2013; 14: 541-54. PubMed PMID: 23556451.

(Review of genetic associations of serum ALT and bilirubin elevations during therapy with tyrosine kinase inhibitors focusing on lapatinib and pazopanib; palbociclib is not discussed).

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf 2013; 36: 491-503. PubMed PMID: 23620168.

(Review of the hepatotoxicity of 18 tyrosine kinase inhibitors approved for use in cancer in the US as of 2013, before the availability of palbociclib which is not discussed).

Dickson MA, Tap WD, Keohan ML, D'Angelo SP, Gounder MM, Antonescu CR, Landa J, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol 2013; 31: 2024-8. PubMed PMID: 23569312.

(Among 30 patients with liposarcoma treated with palbociclib adverse events included neutropenia [50%], thrombocytopenia [30%] and anemia [17%], with no mention of ALT elevations or hepatotoxicity).

Vaughn DJ, Hwang WT, Lal P, Rosen MA, Gallagher M, O'Dwyer PJ. Phase 2 trial of the cyclin-dependent kinase 4/6 inhibitor palbociclib in patients with retinoblastoma protein-expressing germ cell tumors. Cancer 2015; 121: 1463-8. PubMed PMID: 25522918.

(Among 30 patients with germ cell tumors treated with palbociclib, response rates were poor and toxicities were largely hematologic; no mention of ALT elevations or hepatotoxicity).

Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, Zirkelbach JF, et al. FDA Approval: Palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clin Cancer Res 2015; 21: 4760-6. PubMed PMID: 26324739.

(Review of the studies of clinical efficacy and safety that led to the FDA approval of palbociclib; mentions that adverse events were common and led to dose reduction in 36% and discontinuation in 8% of patients; no mention of ALT elevations or hepatotoxicity).

Mangini NS, Wesolowski R, Ramaswamy B, Lustberg MB, Berger MJ. Palbociclib: a novel cyclin-dependent kinase inhibitor for hormone receptor-positive advanced breast cancer. Ann Pharmacother 2015; 49: 1252-60. PubMed PMID: 26324355.

(Review of the structure, mechanism of action, pharmacology, clinical efficacy and safety of palbociclib as therapy of metastatic breast cancer, discusses neutropenia and infections but does not mention ALT elevations or hepatotoxicity).

Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, 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. PubMed PMID: 25524798.

(Among 165 women with metastatic breast cancer [ER+, HER2-] treated with letrozole with or without palbociclib for an average of 28 months, progression-free survival was longed with palbociclib, but side effects including neutropenia were more frequent and severe; no mention of ALT elevations or hepatotoxicity).

Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, et al; PALOMA3 Study Group. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2015; 373: 209-19. PubMed PMID: 26030518.

(Among 521 women with advanced breast cancer [ER+, HER2-] treated with letrozole and either palbociclib or placebo for up to 1 year, progression-free survival was prolonged by adding palbociclib [9.2 vs 3.8 months] and side effects were more common including neutropenia [62% vs 1%] and fatigue [38% vs 26%]; no mention of ALT elevations or hepatotoxicity).

DeMichele A, Clark AS, Tan KS, Heitjan DF, Gramlich K, Gallagher M, Lal P, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clin Cancer Res 2015; 21: 995-1001. PubMed PMID: 25501126.

(Among 37 women with metastatic breast cancer [ER+, HER2-] treated with palbociclib, adverse events [largely hematologic] were common, but rarely led to dose interruption; no mention of ALT elevations or hepatotoxicity).

Palbociclib (Ibrance) for metastatic breast cancer. Med Lett Drugs Ther 2015; 57 (1475): 115-6. PubMed PMID: 26262882.

(Concise review of efficacy and safety of palbociclib as therapy for metastatic breast cancer, mentions frequency of severe neutropenia and risk of septicemia; no mention of hepatotoxicity or ALT elevations).