Hosp Pharm 2015;50(7):578–582
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www.hospital-pharmacy.com
doi: 10.1310/hpj5007-578

Cancer Chemotherapy Update

Lenvatinib and Palbociclib

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The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net.

Name:	Lenvatinib
Synonyms:	*Lenvima;* E7080

MECHANISM OF ACTION

Lenvatinib is a tyrosine kinase inhibitor that reacts with a number of targets including vascular endothelial growth factor receptor (VEGFR)-1 (Flt-1), VEGFR-2 (KDR), VEGFR-3 (Flt-4), fibroblast growth factor receptor (FGFR)-1, platelet-derived growth factor (PDGF) β, and c-KIT. Lenvatinib decreases phosphorylation of VEGFR-2 and inhibits the growth of vascular endothelial cells and formation of vascular-like structures.[1-3]

PHARMACOKINETICS

Over a dose range of 0.5 mg to 20 mg orally (PO) twice a day, the time to maximum concentration (T_{max}) ranges from 1 to 5 hours; the maximum concentration (C_{max}) is 2.5 ng/mL to 674 ng/mL.[4] The 24-hour area under the time versus concentration curve (AUC) was 41 ng•h/mL to 4751 ng•h/mL.[4] The elimination half-life ($T_{½}$) was 46.9 hours to 31.6 hours.[4]

For single daily oral doses of 0.2 mg to 32 mg, the T_{max} was 1.5 to 6.4 hours; the C_{max} was 0.7 to 681.5 ng/mL.[5] The 24-hour AUC was 14.0 ng•h/mL to 5093.5 ng•h/mL.[5] The $T_{½}$ was 5.3 to 18.2 hours.[5]

For oral doses of 4 or 6 mg twice daily, the mean T_{max} was 4.18 and 4.27 hours; the C_{max} was 97.5 and 138 ng/mL respectively.[6] The mean AUC was 692 ng•h/mL and 848 ng•h/mL.[6]

The capsule formulation is reported to have about 10% lower C_{max} and 14% lower AUC than the tablet formulation.[7]

Following continuous oral dosing with 24 mg daily, the T_{max} is 1 to 4 hours; following a high-fat meal, this is delayed to 2 to 4 hours. The AUC increased proportionally with dose from 3.2 to 32 mg. Lenvatinib is 98% to 99% protein bound. Lenvatinib is metabolized in the liver, primarily by CYP3A and aldehyde oxidase. Sixty-four percent is excreted in the feces; 25% is excreted in the kidney. The elimination half-life ($T_{½}$) is 28 hours.[8] Lenvatinib is highly (97% to 99%) protein-bound.[4,8]

Selected therapeutic regimens of lenvatinib appear in **Table 1**.

PREPARATION

1. Lenvatinib is available as 4 mg and 10 mg capsules.
2. The product is packaged in 5-day dose cards of 10 mg, 14 mg, 20 mg, and 24 mg/day.

STABILITY

1. The drug should be stored at room temperature 25°C (77°F).
2. Brief (less than 24 hours) exposure to temperatures up to 30°C (86°F) is acceptable.

ADMINISTRATION

1. Lenvatinib is administered orally; usually once a day.

Table 1. Selected therapeutic regimens of lenvatinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
20 mg	PO	Daily	28 days	560 mg	5, 11, 14, 15
20 mg bid	PO	1 through 14	21 days	560 mg	4, 9
24 mg[a]	PO	Daily	28 days	672 mg	8, 10-14, 16-22
25 mg	PO	Daily	28 days	700 mg	5
32 mg	PO	Daily	28 days	896 mg	5

Note: bid = twice a day; PO = oral.
[a]Conforms to dosing information listed in the manufacturer's labeling.

2. Administration with a high-fat meal has no effect on overall AUC, but absorption is slowed.[7]
3. Lenvatinib can be administered with, or without, food.[7,8]

TOXICITIES (24 MG DAILY)

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

A. **Cardiovascular:** Edema, peripheral 11%,[18] (grade 3 or 4) 0.4%[18]; hypertension 48% to 68%,[13,15-17] (grade 3) 4% to 17%,[13,15,19] (grade 3 or 4) 33% to 42%.[15,17,18]
B. **Central Nervous System:** Headache 26% to 27%,[17,18] (grade 3 or 4) 1% to 3%.[17,18]
C. **Constitutional:** Dysphonia 24% to 27%,[17,18] (grade 3 or 4) 1%[18]; fatigue 42% to 100%,[10,11,13,15-18] (grade 3) 5% to 13%,[11,13,15,16] (grade 3 or 4) 9% to 42%[17,18]; weight loss 32% to 46%,[13,15,18] (grade 3) 3% to 4%,[13,15] (grade 3 or 4) 10%.[18]
D. **Dermatologic:** Alopecia 11%[18]; rash 16% to 50%,[10,18] (grade 3 or 4) 0.4%.[18]
E. **Endocrine/Metabolic:** Hypocalcemia 7%,[18] (grade 3 or 4) 3%[18]; hypothyroidism 46%.[11]
F. **Gastrointestinal:** Anorexia 35% to 50%,[10,11,13,16-18] (grade 3) 2% to 5%,[13,15,16] (grade 3 or 4) 5%[18]; constipation 15% to 50%,[10,18] (grade 3 or 4) 0.4%[18]; diarrhea 35% to 59%,[10,11,13,15-18] (grade 3) 5%,[11,13,15,16] (grade 3 or 4) 2% to 8%[17,18]; dysgeusia 17%[18]; dyspepsia 10%[18]; mucosal inflammation 100%[10]; nausea 32% to 50%,[10,11,16-18] (grade 3) 3%,[16] (grade 3 or 4) 2% to 3%[17,18]; stomatitis 36%,[18] (grade 3 or 4) 4%[18]; vomiting 28% to 50%,[10,11,18] (grade 3) 2%,[17] (grade 3 or 4) 2%[18]; xerostomia 14%,[18] (grade 3 or 4) 0.4%.[18]
G. **Hematologic:** Thrombocytopenia 32%.[11]
H. **Infection:** Pneumonia (grade 3 or 4) 9%.[19]
I. **Musculoskeletal:** Arthralgia 18%[18]; myalgia 15%,[18] (grade 3 or 4) 2%.[18]
J. **Neurologic:** Palmar-plantar erythrodysesthesia 32%,[18] (grade 3 or 4) 3%.[18]
K. **Pain:** Abdominal 12%,[18] (grade 3 or 4) 0.4%[18]; oropharyngeal 10%,[18] (grade 3 or 4) 0.4%[18]; upper abdominal 13%.[18]
L. **Pulmonary:** Dyspnea 50%,[10] (grade 3 or 4) 9%[19]; embolism (grade 3 or 4) 3%.[18]
M. **Renal:** Proteinuria 26% to 58%,[11,13,15,17,18] (grade 3) 2% to 7%,[13,15] (grade 3 or 4) 4% to 10%.[17,18]

DOSE ADJUSTMENT

A. **Hepatic**
   1. Mild or moderate hepatic impairment, no dose adjustment is required.[8]
   2. Severe hepatic impairment, reduce dose to 14 mg daily.[8]
   3. Child-Pugh A or B, reduce dose to 10 mg daily.[20,21]

4. Child-Pugh C, reduce dose to 8 mg daily.[20]
5. Due to the limited number of dosage forms commercially available, the recommended 8 mg and 12 mg doses would be difficult to administer.

B. Renal

1. Mild or moderate renal impairment, no dose adjustment is required.[8]
2. Severe renal impairment, reduce dose to 14 mg daily.[8]

Name:	Palbociclib
Synonyms:	*Ibrance;* PD 0332991

MECHANISM OF ACTION

Cyclin dependent kinases (CDK) 4 and 6, with cyclin D (an activating subunit), promote progression of the cell cycle from the G_1 to the S phase by phosphorylating the retinoblastoma (Rb) protein.[22] Palbociclib is a reversible inhibitor of CDK 4 and 6. Inhibition of CDK 4 and 6 by palbociclib results in cell-cycle arrest in the G_1 phase.[23,24]

PHARMACOKINETICS

For doses of 100 mg to 225 mg daily, the mean T_{max} was 4 to 7 hours; the C_{max} was 44 to 186 ng/mL.[25] The AUC was 333 to 1491 ng•h/mL.[25]

For single doses of 25 mg to 150 mg, the T_{max} was 4 to 7 hours; C_{max} was 10 to 91 ng/mL.[26] The AUC was 58 to 641 ng•h/mL.[26] For daily doses of 25 mg to 150 mg/day, the T_{max} was 4 to 7 hours; C_{max} was 16 to 128 ng/mL.[26] The AUC was 119 to 1084 ng•h/mL.[26]

The volume of distribution (V_d) is 2583 L; the drug is 85% protein bound. Palbociclib is metabolized in the liver primarily by oxidation and sulfonation via CYP3A and SULT2A1; acylation and glucuronidation also occur. The major metabolite in circulation is glucuronide palbociclib conjugate. About 17.5% of a dose is excreted renally, primarily as metabolites. About 74.1% is excreted in the feces, primarily as sulfamic acid palbociclib conjugate. Oral clearance of palbociclib is 63.1 L/h; the mean plasma $T_{½}$ is 29 hours.[27]

Selected therapeutic regimens of palbociclib appear in **Table 2**.

PREPARATION

1. Palbociclib is available as 75 mg, 100 mg, and 125 mg capsules.

STABILITY

1. The drug should be stored at room temperature 20°C to 25°C (68° to 77°F).
2. Brief (less than 24 hours) exposure to temperatures between 15° and 30°C (59° to 86°F) is acceptable.

ADMINISTRATION

1. Palbociclib is administered orally; usually once a day.
2. Palbociclib should be taken with food.
3. Patients should be advised to avoid grapefruit and grapefruit juice.

TOXICITIES (125 MG DAYS 1 THROUGH 21 EVERY 28 DAYS)

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_

Table 2. Selected therapeutic regimens of palbociclib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
25 mg	PO	1 through 21	28 days	525 mg	26
50 mg	PO	1 through 21	28 days	1050 mg	26
75 mg	PO	1 through 21	28 days	1575 mg	26
125 mg[a]	PO	1 through 21	28 days	2625 mg	26-33
150 mg	PO	1 through 21	28 days	3150 mg	25

Note: PO = oral.
[a]Conforms to dosing information listed in the manufacturer's labeling

QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

A. Central Nervous System: Dizziness 10% to 12%[28,29]; headache 12% to 14%.[28,29]

B. Constitutional: Asthenia 11%,[29] (grade 3) 2%[29]; fatigue 35% to 36%,[28,29] (grade 3) 2%,[29] (grade 4) 2%[29]; hot flush 21%.[29]

C. Dermatologic: Alopecia 22%.[29]

D. Endocrine/Metabolic: Hypophosphatemia (grade 3) 12%.[28]

E. Hematologic: Anemia 12% to 29%,[28,29] (grade 3) 5%,[29] (grade 4) 1%[29]; epistaxis 11%[29]; leukopenia 12% to 24%,[28,29] (grade 3) 19%,[29] (grade 4) 6%[28]; neutropenia 20% to 41%,[28,29] (grade 3) 24% to 40%,[28,29,31] (grade 3 or 4) 19%,[30] (grade 4) 6% to 12%[28,29]; neutropenic fever (grade 3) 6%[33]; thrombocytopenia 14% to 29%,[28,29] (grade 3) 2% to 18%,[28-30] (grade 4) 6%.[28]

F. Gastrointestinal: Anorexia 14%,[29] (grade 3) 1%[29]; constipation 12%[29]; diarrhea 17% to 18%,[28,29] (grade 3) 4% to 6%[28,29]; nausea 12% to 23%,[28,29] (grade 3) 2%[29]; stomatitis 12%[29]; vomiting 14%.[29]

H. Hepatic: Increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (grade 3) 11%[33]; transaminitis (grade 3 or 4) 6%.[30]

G. Infection: Influenza 10%,[29] (grade 3) 1%[29]; upper respiratory tract 10%,[29] (grade 3) 1%.[29]

H. Musculoskeletal: Arthralgia 22%,[29] (grade 3) 1%[29]; rhabdomyolitis (grade 3 or 4) 6%.[29]

I. Neurologic: Peripheral neuropathy 10%.[29]

J. Oral: Nasopharygitis 16%.[29]

K. Pain: Back 13%,[29] (grade 4) 1%[29]; bone 10%,[29] (grade 3) 1%,[29] (grade 4) 1%[29]; in extremity 10%[29]; musculoskeletal 10%,[29] (grade 3) 1%[29]; oropharyngeal 10%.[29]

L. Pulmonary: Cough 12%[29]; dyspnea 13%,[29] (grade 3) 2%.[29]

DOSE ADJUSTMENT

A. Hepatic

1. Bilirubin less than or equal to the upper limit of normal (ULN) and AST greater than the ULN, no dose adjustment required.[27]
2. Bilirubin greater than 1 to 1.5 times the ULN, no dose adjustment required.[27]
3. Bilirubin greater than 1.5 times the ULN, no information available.[27]

B. Renal

1. Creatinine clearance greater than or equal to 60 mL/min, no dose adjustment required.[27]
2. Creatinine clearance less than 60 mL/min, no information available.[27]

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