Cancer Chemotherapy Update

Gefitinib and Sonidegib

Corey J. Medler, BA*; J. Aubrey Waddell, PharmD, FAPhA, BCOP; and
Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP

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:	Gefitinib
Synonyms:	Iressa, ZD1839

MECHANISM OF ACTION

Gefitinib is a small molecule selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that provides antitumor activity.^{1,2} The EGFR is one of the main components in regulating normal cell growth.¹ Proliferation and survival of cancer cells can result from specific signal transduction pathways that are blocked by gefitinib.² One advantage for gefitinib is that it causes minimal damage to normal cell function, because in malignant cancer cells it can inhibit specific deregulated pathways.²

Patients should be selected based on the presence of EGFR exon 19 deletion or substitution mutation of exon 21.³ These mutations are commonly found in subpopulations of non-small-cell lung cancer (NSCLC) such as persons of East Asian origin, females, and nonsmokers with adenocarcinoma tumors.⁴

PHARMACOKINETICS

A single 50 mg dose of gefitinib has a maximum plasma concentration (C_{max}) of 31 ng/mL, a mean

time to maximum concentration (t_{max}) of 3 hours, a mean area under the time versus concentration curve (AUC_{0-24h}) of 378 ng•h/mL, and a terminal half life ($t_{1/2}$) of 38 hours.² A single dose of 100 mg has a C_{max} of 43 ng/mL, a mean t_{max} of 4 hours, a mean AUC_{0-24h} of 531 ng•h/mL, and a mean $t_{1/2}$ of 35 hours.² A 225 mg dose has a C_{max} of 150 ng/mL, a mean t_{max} of 4 hours, a mean AUC_{0-24h} of 1,986 ng•h/mL, and a mean $t_{1/2}$ of 30 hours.² Multiple doses of 50 mg, 100 mg, and 225 mg demonstrated a C_{max} of 60, 105, and 341 ng/mL, respectively; a median t_{max} range of 5 to 6 hours; a mean AUC_{0-24h} of 1,021 ng•h/mL to 5,191 ng•h/mL; and a mean $t_{1/2}$ of 52, 45, and 40 hours, respectively.² Multiple doses of 400 to 700 mg have a mean C_{max} range of 779 ng/mL to 1,156 ng/mL, a mean t_{max} of 3 to 5 hours, a mean AUC_{0-24h} range of 11,399 ng•h/mL to 21,580 ng•h/mL, and a mean $t_{1/2}$ of 45 hours to 55 hours.²

Selected therapeutic regimens of gefitinib are listed in Table 1.

PREPARATION

A. Gefitinib is available as a 250 mg tablet.

STABILITY

A. Gefitinib should be stored at controlled room temperature (20°C–25°C [68°F–77°F]).

*Corey J. Medler is a doctor of pharmacy candidate at the University of Tennessee College of Pharmacy.

Table 1. Selected therapeutic regimens of gefitinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/ cycle	References
250 mg ^a	PO	1 through 28	28	7,000 mg	3-7
500 mg	PO	1 through 28	28	14,000 mg	6

Note: PO = oral.

^aConforms to dosing information listed in the manufacturer's labeling.

ADMINISTRATION

A. Gefitinib is administered by mouth once daily, with or without food.

B. Patients with difficulty swallowing may submerge the tablet in 4 to 8 ounces of water and stir for approximately 15 minutes. The resulting suspension is swallowed or administered via feeding tube. The container is rinsed with 4 to 8 ounces of water and the solution is swallowed or administered via feeding tube immediately.³

TOXICITIES

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 they 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: Cardiac failure (all grades) 3%, (grade 3 or 4) 2%⁵; fluid retention (grade 1 or 2) 7%⁶; hypertension (all grades) 8%⁵; peripheral edema (all grades) 4%, (grade 3 or 4) 0.1%⁷; prolongation of PR interval (grade 1) 3%².

B. Central Nervous System: Dizziness (all grades) 7%⁸; headache (grade 1 or 2) 15%, (grade 3) 1%¹.

C. Constitutional: Asthenia (all grades) 13%⁶ (grade 1 or 2) 8% to 25%^{1,4,7,9} (grade 3 or 4) 3% to 10%^{1,4,6,7}; fatigue (all grades) 22%⁸; pyrexia (grade 1 or 2) 7% to 10%, (grade 3 or 4) 0.3% to 1%^{6,7}; somnolence (grade 1 or 2) 18%, (grade 3) 3%¹.

D. Dermatologic: Acneiform rash (grade 1 or 2) 13% to 63%^{1,2,4,6,8,9} (grade 3 or 4) 1% to 4%^{1,4,6,8-10}; alopecia (all grades) 3%^{2,6}; dermatitis acneiform (all grades) 7%⁵; dry skin (grade 1 or 2) 7% to 27%^{1,5-7,9,10}; paronychia (all grades) 3%, (grade 3 or 4) 0.1%⁷; pruritus (all grades) 8% to 31%⁷⁻¹⁰ (grade 3 or 4) 0.3%⁷; rash (all grades) 37% to 45%^{5,7} (grade 3 or 4) 2%⁷; seborrhea (grade 1 or 2) 20%².

E. Eye Disorder: Corneal disease (all grades) 13%²; eye disorders (all grades) 6%²; keratitis and blepharitis (all grades) 10%².

F. Gastrointestinal: Anorexia (grade 1 or 2) 5% to 32%^{1,2,9,10} (grade 3 or 4) 1% to 2%^{4,6,10} (all grades) 10%⁷; constipation (grade 1 or 2) 7% to 11%^{4,6} (grade 3 or 4) 1%^{4,6}; diarrhea (grade 1 or 2) 20% to 49%^{2,5,9} (grade 3 or 4) 4% to 9%^{1,6-8,10}; nausea (grade 1 or 2) 10% to 33%^{2,5,8-10} (grade 3 or 4) 1% to 3%^{1,6,7,9,10}; pharyngitis (grade 1 or 2) 16%¹; stomatitis (grade 1 or 2) 6% to 9%^{6,7} (grade 3 or 4) 0.2%⁷; vomiting (grade 1 or 2) 6% to 34%^{1,2,5,9} (grade 3 or 4) 1% to 3%^{6,7,10}; xerostomia (grade 1 or 2) 18%¹.

G. Hematologic: Anemia (grade 1 or 2) 4% to 5%^{6,10} (grade 3 or 4) 2%^{6,10}; febrile neutropenia (grade 1 or 2) 1%, (grade 3 or 4) 1%⁶; neutropenia (grade 1 or 2) 5%^{6,10} (grade 3 or 4) 2% to 6%^{6,10}.

H. Hepatic: Alanine aminotransferase (ALT) increased (all grades) 8%⁵ (grade 1 or 2) 10% to 11%^{2,9} (grade 3) 10%² (grade 3 or 4) 1% to 2%^{5,9}; alkaline phosphatase increased (grade 1 or 2) 10%²; aspartate aminotransferase (AST) increased (all grades) 6%⁵ (grade 1 or 2) 10% to 11%^{2,9} (grade 3) 10%².

I. Infection: Infection (all grades) 16%, (grade 3 or 4) 2%⁸; lower respiratory tract infection and lung infection (grade 1 or 2) 10%, (grade 3 or 4) 3%⁶; pneumonia (all grades) 4%, (grade 3 or 4) 3%^{5,7}; urinary tract infection (all grades) 7%⁵.

J. Neurologic: Neurotoxicity (grade 1 or 2) 7%, (grade 3 or 4) 0.1%⁶; sensory neuropathy (all grades) 17%⁸.

K. Pain: Abdominal pain (grade 1 or 2) 17%, (grade 3) 3%¹; cancer pain (all grades) 4%, (grade 3 or 4) 1%⁷; chest pain (all grades) 18%⁸; myalgia (grade 1 or 2) 3%, (grade 3 or 4) 0.1%.⁶

L. Pulmonary: Cough increased (grade 1 or 2) 7% to 37%,^{5,8} (grade 3) 1%^{1,6-8}; dyspnea (grade 1 or 2) 7% to 19%,^{1,6-8} (grade 3 or 4) 3% to 6%^{1,6,7}; hemoptysis (all grades) 5%, (grade 3 or 4) 0.4%⁷; interstitial lung disease (all grades) 1%⁵; interstitial pneumonitis (all grades) 2%, (grade 3 or 4) 2%.⁸

M. Treatment-Related Death: Death from any adverse event considered drug-related 1% to 5%.^{6,7}

DOSAGE MODIFICATIONS

A. Hepatic: Patients with mild hepatic impairment had a mean systemic exposure increase by 40%, patients with moderate hepatic impairment increased by 263%, and patients with severe impairment increased by 166%. Hold gefitinib for up to 14 days for any grade 2 or higher AST or ALT elevations. Discontinue gefitinib for severe hepatic impairment.³

B. Renal: No dosage reductions are necessary for renal impairment.^{1,3,9}

Name: Sonidegib

Synonyms: Erismodegib, Odomzo, LDE225

MECHANISM OF ACTION

Sonidegib displays antitumor activity by inhibiting the hedgehog signaling pathway. Specifically it selectively inhibits the positive regulator component of the hedgehog pathway known as Smoothed (SMO).^{11,12} In the postnatal period through adulthood, the hedgehog pathway is instrumental in the regulation of bone development, tissue maintenance and repair, and maintenance of some stem cell populations such as those in hair follicles.¹¹ A mutation in SMO leads to the activation of the ligand-independent pathway and has been shown to

result in basal cell carcinoma, medulloblastoma, and rhabdomyosarcoma.¹²

PHARMACOKINETICS

Following oral administration, sonidegib has a median t_{max} of 2 hours (range, 1-48 hours).¹¹ For single doses of 100 mg to 400 mg, the mean C_{max} was 85.8 to 267 ng/mL, mean AUC_{0-168h} was 1,880 ng•h/mL to 7,450 ng•h/mL, and median t_{max} was 2 to 4 hours.¹¹ For single doses of 800 mg to 3,000 mg, the mean C_{max} range was 430 ng/mL to 429 ng/mL, mean AUC_{0-168h} range was 7,870 ng•h/mL to 11,800 ng•h/mL, and median t_{max} range was 4 to 2 hours.¹¹ On day 15 following a dose of 100 mg to 400 mg once daily, the mean C_{max} was 155 ng/mL to 558 ng/mL, mean AUC_{0-24h} was 2,690 ng•h/mL to 10,200 ng•h/mL, and median t_{max} was 4 to 13 hours.¹¹ On day 15 following a dose of 800 mg to 3,000 mg once daily, the mean C_{max} was 840 ng/mL to 1,670 ng/mL, mean AUC_{0-24h} was 12,800 ng•h/mL to 24,600 ng•h/mL, and median t_{max} was 2 hours to 5 hours.¹¹ Steady state was achieved in 2 to 24 weeks of repeated dosing of sonidegib, with an effective median elimination $t_{1/2}$ estimated to be about 11 days.¹¹

Selected therapeutic regimens of sonidegib are listed in Table 2.

PREPARATION

A. Sonidegib is available as a 200 mg capsule.

STABILITY

A. Sonidegib should be stored at 20°C-25°C (68°F-77°F).

B. Brief (<24 hour) exposure to temperatures down to 15°C (59°F) and up to 30°C (86°F) is acceptable.¹³

ADMINISTRATION

A. Sonidegib is administered by mouth once daily.

B. Sonidegib should be taken on an empty stomach, a minimum of 1 hour before or 2 hours after a meal.¹³

Table 2. Selected therapeutic regimens of sonidegib

Daily dose	Route/ frequency of administration	Administered on day(s)	Cycle length	Total dose/ cycle	References
200 mg ^a	PO	1 through 28	28 days	5,600 mg	9, 10
800 mg	PO	1 through 28	28 days	22,400 mg	9

Note: PO = oral.

^aConforms to dosing information listed in the manufacturer's labeling.

TOXICITIES

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 they 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: Atrial fibrillation (grade 3 or 4) 1%¹²; hypertension (all grades) 6%, (grade 3 or 4) 3%¹²; hypotension (all grades) 3%, (grade 3 or 4) 1%¹².

B. Central Nervous System: Headache (all grades) 15%.¹²

C. Constitutional: Asthenia (all grades) 8%, (grade 3 or 4) 3%¹²; fatigue (all grades) 28%¹²; fatigue/asthenia (all grades) 41%.¹¹

D. Dermatologic: Alopecia (all grades) 12% to 43%,^{11,12} (grade 3 or 4) 9%.¹²

E. Endocrine/metabolic: Amylase increased (grade 3 or 4) 1%¹²; blood creatine kinase increased (all grades) 12% to 29%,^{11,12} (grade 3 or 4) 6%.¹²

F. Gastrointestinal: Anorexia (all grades) 24%¹¹; appetite decreased (all grades) 19%¹²; constipation (all grades) 6% to 8%,^{11,12} (grade 3 or 4) 1%¹²; diarrhea (all grades) 24%¹²; dysgeusia (all grades) 12% to 38%^{11,12}; nausea (all grades) 24% to 33%,^{11,12} (grade 3 or 4) 1%¹²; vomiting (all grades) 6% to 12%,^{11,12} (grade 3 or 4) 1%¹²; weight decreased (all grades) 27%, (grade 3 or 4) 1%.¹²

G. Hematologic: Anemia (all grades) 3%.¹²

H. Hepatic: ALT increased (grade 3 or 4) 1%¹²; AST increased (grade 3 or 4) 1%¹²; lipase increased (all grades) 8%, (grade 3 or 4) 5%.¹²

I. Infection: Pneumonia (all grades) 6%.¹²

J. Musculoskeletal: Arthralgia (all grades) 13%, (grade 3 or 4) 1%¹²; muscle spasms (all grades) 24% to 49%,^{11,12} (grade 3 or 4) 3%¹²; myalgia (all grades) 6% to 19%^{11,12}; rhabdomyolysis (grade 3 or 4) 1%.¹²

K. Respiratory: Dyspnea (all grades) 12%.¹¹

DOSAGE MODIFICATIONS

A. Hepatic: No dose adjustment recommended for mild hepatic impairment, or defined as AST greater than

upper limit of normal (ULN) or total bilirubin greater than 1 to 1.5 times ULN. There is no information available regarding moderate or severe hepatic impairment.¹³

B. Renal: No dose adjustment is recommended for renal impairment.¹³

REFERENCES

- Baselga J, Rischin D, Ranson M, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol*. 2002;20(21):4292-4302.
- Nakagawa K, Tamura T, Negoro S, et al. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (*Iressa*, ZD1839) in Japanese patients with solid malignant tumors. *Ann Oncol*. 2003;14(6):922-930.
- Iressa* [prescribing information]. Cheshire, England: AstraZeneca UK, 2015. <http://www.azpicentral.com/iressa/iressa.pdf#page=1>. Accessed August 17, 2015.
- Chen A, Solimando D, Waddell J. Gefitinib, fluorouracil, oxaliplatin and leucovorin (IFOX) regimen for colorectal cancer. *Hosp Pharm*. 2013;48(11):905-911.
- Douillard J, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: A phase-IV, open-label, single-arm study. *Br J Cancer*. 2014;110(1):55-62.
- Kim E, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): A randomised phase III trial. *Lancet*. 2008;372(9652):1809-1818.
- Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicenter study (*Iressa* survival evaluation in lung cancer). *Lancet*. 2005;366(9496):1527-1537.
- Sun J, Lee K, Kim S, et al. Gefitinib versus pemetrexed as second-line treatment in patients with nonsmall cell lung cancer previously treated with platinum-based chemotherapy (KCSG-LU08-01). *Cancer*. 2012;118(24):6234-6242.
- Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2003; 21(12):2237-2246.
- Giaccone G, Johnson DH, Manegold C, et al. A phase III clinical trial ZD1839 ("Iressa") in combination with gemcitabine and cisplatin in chemotherapy-naïve patients with advanced non-small cell lung cancer (INTACT-1). *J Clin Oncol*. 2004; 22(5):777-784.
- Rodon J, Tawbi HA, Thomas AL, et al. A phase I, multicenter, open-label, first-in-human, dose-escalation study of

the oral smoothened inhibitor sonidegib (LDE225) in patients with advanced solid tumors. *Clin Cancer Res* 2014;20(7):1900-1909.

12. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): A multi-

center, randomised, double-blind phase 2 trial. *Lancet Oncol*. 2015;16(6):716-728.

13. *Odomzo* [prescribing information]. East Hanover, NJ: NovartisPharmaceuticalCorp;2015.http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205266s0001b1.pdf. Accessed August 17, 2015. ■