Cancer Chemotherapy Update

Drug Monographs: Afatinib and Obinutuzumab

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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 Boulevard #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: Afatinib
Synonyms: Gilotrif, BIBW2992

MECHANISM OF ACTION

Afatinib is an aniline-quinazoline derivative that is a highly selective, potent, and irreversible inhibitor of both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER2) kinases.¹ It covalently binds to EGFR, HER2, HER3, and HER4 and irreversibly blocks signaling from the molecules.^{2,3} Afatinib is active against an array of EGFR mutations that have been shown to be resistant to first-generation EGFR tyrosine kinase inhibitors.^{1,4,5}

PHARMACOKINETICS

Following oral administration of afatinib 40 mg every 24 hours, steady state is reached at 7 days.^{1,6} The median time to peak plasma concentration (T_{max}) is 5.49 hours after the first dose¹ and 2.5 to 2.95 hours at steady state.^{1,6} The geometric mean area under the plasma concentration-time curve (AUC) at steady state is 968 ng•h/mL.¹ The mean maximum plasma concentration (C_{max}) is 21.1 ng/mL after the first dose¹ and 29 ng/mL to 63.4 ng/mL at steady state.^{1,6} Administration of afatinib with a high-fat meal causes a 51% decrease in C_{max} , a 37% decrease in AUC, and a 3.88 hour increase in T_{max} compared to

fasting administration.¹ Afatinib is 65% to 77% protein bound,² with an apparent volume of distribution (V_d) of 2,220 to 3,150 L at steady state.¹ Eighty-nine percent of a dose is eliminated as the parent compound.² The mean terminal half life ($t_{1/2}$) is 34 to 37.2 hours; the apparent clearance (CL) is 689 to 1,340 L/min.^{1,6} Eighty-five percent of afatinib is eliminated in the feces, and 4% is eliminated in the urine.²

Selected therapeutic regimens of afatinib appear in Table 1.

PREPARATION

- Follow institutional policies for the preparation of hazardous medications when dispensing afatinib.
- Afatinib is available as 20 mg, 30 mg, and 40 mg tablets.
- The manufacturer recommends afatinib be dispensed in the original bottle to protect from high humidity and light.

STORAGE

- Store at 25°C (77°F).
- Brief (less than 24 hours) exposure to temperatures up to 30°C (86°F) is acceptable.

ADMINISTRATION

- Afatinib is taken orally (PO) once a day.
- Afatinib should be taken at least 1 hour before or 2 hours after a meal.

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Table 1. Selected therapeutic regimens of afatinib

Dose	Route of administration	Administered	Cycle length	Total dose per month	References
40 mg	PO	Daily	–	1,200 mg	1, 3, 6-8 ^a
50 mg	PO	Daily	–	1,500 mg	1, 3-5

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 make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percentage unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Epistaxis (grade 1 or 2) 13%,⁷ (grade 1) 16% to 30%.^{3,6}
- B. Constitutional:** Fatigue (grade 1 or 2) 16%,⁷ (grade 3 or 4) 1%,⁷ (grade 1) 17% to 21%,^{3,6} (grade 2) 5% to 7%,^{3,6} (grade 3) 3% to 5%.^{3,6}
- C. Dermatologic:** Cheilitis (grade 1 or 2) 12%⁷; dermatitis acneiform (grade 1) 8% to 32%,^{1,6} (grade 2) 16%⁶; dry skin/xerosis (grade 1 or 2) 29%,⁷ (grade 1) 3% to 20%,^{1,3,6} (grade 2) 3% to 7%,³ (grade 3 or 4) 0.4%⁷; lip effects (grade 1) 7%³; paronychia/nail effects (grade 1 or 2) 45%,⁷ (grade 3 or 4) 11%,⁷ (grade 1) 27%,³ (grade 2) 47%,³ (grade 3) 7%³; pruritis (grade 1 or 2) 18%,⁷ (grade 1) 37%,³ (grade 2) 10%,³ (grade 3 or 4) 0.4%⁷; rash (grade 1) 32%,⁶ (grade 2) 5%⁶; erythematous rash (grade 1) 11% to 38%,^{1,6} (grade 2) 31%,¹ (grade 3) 4%¹; rash or acne (grade 1 or 2) 73%,⁷ (grade 1) 43%,³ (grade 2) 40%,³ (grade 3) 7%,³ (grade 3 or 4) 16%.⁷
- D. Endocrine/Metabolic:** Weight loss (grade 1) 7%,³ (grade 2) 3%.³
- E. Gastrointestinal:** Constipation (grade 1 or 2) 3%⁷; decreased appetite (grade 1 or 2) 17%,⁷ (grade 1) 13% to 21%,^{3,6} (grade 2) 5% to 13%,^{3,6} (grade 3) 3% to 5%,^{3,6} (grade 3 or 4) 3%⁷; diarrhea (grade 1 or 2) 81%,⁷ (grade 1) 42% to 63%,^{1,3,6} (grade 2) 16% to 27%,^{1,3,6} (grade 3) 7% to 11%,^{1,3,6} (grade

3 or 4) 14%⁷; nausea (grade 1 or 2) 17%,⁷ (grade 1) 13% to 21%,^{1,3,6} (grade 2) 3% to 5%,^{6,3} (grade 3 or 4) 1%⁷; stomatitis/mucositis (grade 1 or 2) 62%,⁷ (grade or 4) 9%⁷; vomiting (grade 1 or 2) 14%,⁷ (grade 1) 8% to 13%,^{1,3} (grade 2) 4%,¹ (grade 3) 3%,³ (grade 3 or 4) 3%.⁷

F. Musculoskeletal: Muscle spasm (grade 1) 3%.³

G. Ophthalmic: Conjunctivitis/dry eye (grade 1) 20%.³

H. Respiratory: Mucosal inflammation (grade 1) 15% to 42%,^{1,6} (grade 2) 8% to 11%^{1,6}; rhinorrhea (grade 1) 23%,³ (grade 2) 3%.³

Name: Obinutuzumab

Synonyms: Gazyva, GA101

MECHANISM OF ACTION

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody that has antibody-dependent cellular cytotoxicity (ADCC) and induces direct cell death.⁹ Glycoengineering, or modification of specific sugar molecules in an antibody, generates new antibody variants with enhanced ability to recruit immune cells. The Fc region of the obinutuzumab antibody has been glycoengineered to reduce fucosylation (ie, addition of fucose sugar to molecule), which increases its affinity for the FcγRIIIa receptor and enhanced ADCC potency.¹⁰

PHARMACOKINETICS

Following a single intravenous (IV) infusion of a 800 mg dose, the mean AUC was 1,470 µg•h/mL, mean C_{max} was 358 µg/mL, mean t_{1/2} was 6.11 days, and mean CL was 347 mL/day.¹¹ Following a 1,200 mg dose, the mean AUC was 1,970 µg•h/mL, mean C_{max} was 415 µg/mL, mean t_{1/2} was 14.5 days, and mean CL was 248 mL/day.¹¹ Following 800 mg on day 1 and 1,200 mg on day 8, the mean AUC was 6540 µg•h/mL, mean C_{max} was 669 µg/mL, mean t_{1/2} was 14.2 days, and mean CL was 108 mL/day.¹¹ Following 800 mg on day 1, 1,200 mg on day 8, and

1,200 mg every 3 weeks for 7 cycles, the mean AUC was 10,800 $\mu\text{g}\cdot\text{h/mL}$, mean C_{max} was 1,040 $\mu\text{g/mL}$, mean $t_{1/2}$ was 27.2 days, and mean CL was 44.1 mL/day.¹¹ The steady state V_d of obinutuzumab is 3.8 L, the CL is 90 mL/day, and the $t_{1/2}$ is 28.4 days.¹² Elimination of obinutuzumab is probably by target mediated drug disposition, which results in faster than linear elimination.¹²

Selected therapeutic regimens of obinutuzumab appear in Table 2.

PREPARATION

- A. Follow institutional policies for preparation of hazardous medications when preparing obinutuzumab.
- B. Use obinutuzumab injection 25 mg/mL.
- C. Dilute in 0.9% sodium chloride:
 1. 100 mg in 250 mL.
 2. 900 mg and 1,000 mg in 250 mL.

- D. The manufacturer recommends that only normal saline be used to dilute the drug. Information concerning compatibility with other diluents is not available.¹²

STABILITY

Solutions in 0.9% sodium chloride are stable for up to 24 hours under refrigeration (2°C to 8°C [36°F to 46°F]).

ADMINISTRATION

- A. Obinutuzumab is administered as an IV infusion.
 1. 100 mg over 4 hours.
 2. 900 mg:
 - a. 50 mg/h for 30 minutes.
 - b. Increase by 50 mg/h every 30 minutes to a maximum rate of 400 mg/h.
 3. 1,000 mg:
 - a. 100 mg/h for 30 minutes.

Table 2. Selected therapeutic regimens of obinutuzumab

Dose	Route of administration	Administered on day(s)	Cycle length	Total dose per cycle	References
Cycle 1: 100 mg 900 mg 1,000 mg	IV	1	28 days	3,000 mg	12, 15 ^a
Cycles 2-6: 1,000 mg		2 8, 15			
Cycle 1: 1,600 mg	IV	1, 8	21 days	3,200 mg	13, 14
Cycles 2-8: 800 mg		1			
Cycle 1: 1,000 mg	IV	1, 7, 14, 21	90 days	4,000 mg	10
Cycles 2-9: 1,000 mg		1			
Cycle 1: 1,200 mg 800 mg	IV	1 8	21 days	2,000 mg	11
Cycles 2-8: 800 mg		1			
Cycle 1: 800 mg 1,200 mg	IV	1 8	21 days	2,000 mg	9
Cycles 2-8: 1,200 mg		1			

Note: IV = intravenous.

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

b. Increase by 100 mg/h every 30 minutes to a maximum rate of 40 mg/h.

B. Obinutuzumab should not be given as an IV push or bolus.

TOXICITIES

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- A. Cardiovascular:** Cerebrovascular accident (grade 1 or 2) 5%,⁹ extrinsic vascular compression (grade 3 or 4) 5%,⁹ peripheral edema (grade 1 or 2) 8% to 14%.^{13,14}
- B. Central Nervous System:** Headache (grade 1 or 2) 5% to 25%,¹⁰⁻¹² (grade 3 or 4) 4%¹⁰; insomnia (grade 1 or 2) 14% to 25%.^{9,11}
- C. Constitutional:** Asthenia (grade 1 or 2) 15% to 32%,^{9,13,14} (grade 3 or 4) 3% to 10%^{9,13,14}; fatigue (grade 1 or 2) 14%^{9,10}; malaise (grade 1 or 2) 17%¹¹; pyrexia (grade 1 or 2) 14% to 23%.^{10,14}
- D. Endocrine/Metabolic:** Hypophosphatemia (grade 1 or 2) 17%,¹¹ (grade 3 or 4) 8%.¹¹
- E. Gastrointestinal:** Abdominal pain (grade 1 or 2) 5% to 10%,^{13,14} anorexia (grade 1 or 2) 19%,⁹ constipation (grade 1 or 2) 10% to 25%,^{11,13} diarrhea (grade 1 or 2) 5% to 24%,^{9-11,13-14} nausea (grade 1 or 2) 14% to 18%.^{9,10,14}
- F. Hematologic:** Anemia (grade 1 or 2) 5% to 33%,^{9,11,13} (grade 3 or 4) 5% to 10%^{9,13}; febrile neutropenia (grade 3 or 4) 5%¹⁴; leukopenia (grade 1 or 2) 50%,¹¹ (grade 3 or 4) 5% to 17%^{9,11}; lymphopenia (grade 3 or 4) 9% to 15%^{9,13,14}; neutropenia (grade 1 or 2) 41%,¹¹ (grade 3 or 4) 10% to 23%^{9-11,13}; thrombocytopenia (grade 1 or 2) 14% to 50%,^{9,11} (grade 3 or 4) 5% to 8%.^{9,11,13}
- G. Hepatic:** Aspartate aminotransferase increase (grade 1 or 2) 33%,¹¹ alanine aminotransferase increase (grade 1 or 2) 33%,¹¹ hyperbilirubinemia

(grade 1 or 2) 17%,¹¹ lactate dehydrogenase increase (grade 1 or 2) 25%.¹¹

- H. Hypersensitivity:** Infusion-related reactions (grade 1 or 2) 55% to 83%,^{9-11,13-14} (grade 3 or 4) 8% to 18%.^{9-11,13-14}
- I. Infection:** (grade 1 or 2) 32% to 52%,^{9,10,14} (grade 3 or 4) 5%.¹⁴
- J. Musculoskeletal:** Axillary pain (grade 3 or 4) 5%,⁹ back pain (grade 1 or 2) 17%,¹¹ pain in extremity (grade 1 or 2) 8%.¹³
- K. Neurologic:** Sciatica (grade 3 or 4) 5%.⁹
- L. Respiratory:** Cough (grade 1 or 2) 5% to 25%,^{10,13,14} nasopharyngitis (grade 1 or 2) 58%.¹¹

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