Cancer Chemotherapy Update

Drug Monographs: Cabozantinib and Omacetaxine

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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@aol.com; 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: Cabozantinib

Synonyms: Cabozantinib s-Malate; XL184; BMS 907351; *Cometriq*

MECHANISM OF ACTION

Cabozantinib is a multi-tyrosine kinase inhibitor that inhibits a variety of targets including RET, MET, vascular endothelial growth factors 1, 2, 3, KIT, TRKB, FLT-3, AXL, and TIE-2. Inhibition of these factors reduces maintenance of the tumor microenvironment, metastases, oncogenesis, and tumor angiogenesis.¹

PHARMACOKINETICS

The maximum serum concentration ($C_{\max}$) of cabozantinib is dose-dependent, ranging from 34.2 to 603 ng/mL following oral doses of 0.08 mg/kg to 1.28 mg/kg.² Cabozantinib is well absorbed orally and has a time to maximum concentration ($T_{\max}$) of 5 hours. The terminal half life is ~55 to 100 minutes.³⁻⁵ Cabozantinib is highly (99.7%) protein-bound and has a volume of distribution (V_d) of 349 L. When taken with food, the area under the time versus concentration curve (AUC) and $C_{\max}$ increase by 57% and 47%, respectively. The drug is metabolized in the liver, by CYP3A4, to XL184 N-oxide. Cabozantinib is excreted hepatically (54%) and renally (27%).⁵

Selected therapeutic regimens of cabozantinib appear in Table 1.

PREPARATION

- Follow institutional policies for preparation of hazardous medications when dispensing cabozantinib.
- Cabozantinib is available as 60 mg, 100 mg, and 140 mg capsules.

STORAGE AND STABILITY

- Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).
- Brief exposure to temperatures from 15°C to 30°C (59°F to 86°F) is acceptable.

ADMINISTRATION

- Cabozantinib is taken orally once a day.
- The drug should be taken on an empty stomach (1 hour before or 2 hours after eating).

TOXICITIES

- 100 mg/day**
 - Cardiovascular:** Hypertension (grade 3 or 4) 5% to 9%.^{6,7,13}
 - Constitutional:** Fatigue (grade 3 or 4) 4% to 19%.^{6-8,10-13}
 - Gastrointestinal:** Constipation 4%,¹³ diarrhea (grade 3 or 4) 3% to 9%,^{8,9,12,13} nausea (grade 3 or 4) 10%.¹¹

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Table 1. Selected therapeutic regimens of cabozantinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month	References
100 mg	PO	Daily	—	3,000 mg	6-13
125 mg	PO	Daily	—	3,750 mg	16
140 mg ^a	PO	Daily	—	4,200 mg	5, 14-19

Note: PO = oral.

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

4. **Hematologic:** Anemia (grade 3 or 4) 10%,¹¹ thrombocytopenia (grade 3 or 4) 9%.⁹
5. **Neurologic:** Asthenia (grade 3 or 4) 7%,¹² hand-foot syndrome (grade 3 or 4) 5% to 15%.^{6-10,12}

B. 140 mg/day

1. **Central Nervous System (CNS):** Convulsion (grade 3 or 4) 9%,¹⁶ headache (grade 3 or 4) 9%.¹⁶
2. **Cardiovascular:** CNS hemorrhage (grade 3 or 4) 2%¹⁵; dehydration (grade 3 or 4) 2%¹⁵; hypertension (grade 1 or 2) 20%,¹⁴ (grade 3 or 4) 5% to 13%^{14,18,19}; increased troponin I and myocarditis (grade 3 or 4) 2%¹⁵; pulmonary embolism (grade 3 or 4) 4% to 12%.^{15,17}
2. **Constitutional:** Decreased weight (grade 1 or 2) 20%,¹⁴ (grade 3 or 4) 3%¹⁴; fatigue (grade 1 or 2) 55%,¹⁴ (grade 3 or 4) 2% to 23%.^{14-16,18}
3. **Dermatologic:** Dry skin (grade 1 or 2) 23%,¹⁴ hair color changes (grade 1 or 2) 28%,¹⁴ rash (grade 1 or 2) 30%.¹⁴
4. **Endocrine/metabolic:** Hypocalcemia (grade 3 or 4) 9%¹⁸; hypophosphatemia (grade 3 or 4) 10% to 23%^{16,17}; increased blood amylase (grade 1 or 2) 10%,¹⁴ (grade 3 or 4) 8%¹⁴; increased lipase (grade 1 or 2) 8%,¹⁴ (grade 3 or 4) 10% to 20%.^{14,16,19}
5. **Gastrointestinal:** Anorexia (grade 1 or 2) 63%,¹⁴ (grade 3 or 4) 3%¹⁴; diarrhea (grade 1 or 2) 63%,¹⁴ (grade 3 or 4) 8% to 20%^{14,16-19}; dysgeusia (grade 1 or 2) 28%¹⁴; mucosal inflammation (grade 1 or 2) 23%,¹⁴ nausea (grade 1 or 2) 50%,¹⁴ (grade 3 or 4) 2% to 3%^{14,15}; oral pain (grade 1 or 2) 25%¹⁴; vomiting (grade 1 or 2) 38%.¹⁴
6. **Hematologic:** Lymphopenia (grade 3 or 4) 9%.¹⁶
7. **Hepatic:** Increased alanine aminotransferase (ALT) (grade 1 or 2) 28%,¹⁴ (grade 3 or 4) 2% to 9%¹⁴⁻¹⁶; increased aspartate aminotransferase (AST) (grade 1 or 2) 28%,¹⁴ (grade 3 or 4) 5%.¹⁴
8. **Neurologic:** Hand-foot syndrome (grade 1 or 2) 28%,¹⁴ (grade 3 or 4) 13% to 20%^{14,18,19}; peripheral neuropathy (grade 1 or 2) 10%.¹⁴

Name: Omacetaxine

Comment: Homoharringtonine is a cephalotaxus alkaloid extracted from the bark of the *Cephalotaxus* species of evergreen tree found in China. Omacetaxine is a semi-synthetic form of homoharringtonine.²⁰ Both compounds have the same chemical structure and Chemical Abstract Service (CAS) registry number (CAS 26833-87-4).²¹

Synonyms: Omacetaxine mepesuccinate; homoharringtonine; *Synribo*; CGX-635

MECHANISM OF ACTION

Omacetaxine reversibly binds to the A-site cleft in the large ribosomal subunit of a type of archaeobacteria, interferes with chain elongation, and inhibits protein synthesis. In vitro, omacetaxine mediates inhibition of Mcl-1 and promotes apoptosis without the binding of Bcr-Abl.²²⁻²⁹

PHARMACOKINETICS

Omacetaxine is rapidly absorbed with a $C_{\max}$ of 25.1 to 36.2 ng/mL and $T_{\max}$ of 0.55 to 0.6 hours. The V_d is 126.8 L/m². The apparent clearance following the first dose is 13.5 L/h/m² and 10.5 L/h/m² at steady state. The mean half-life ($t_{1/2}$) of elimination is 7 hours. After the first dose, the apparent volume of distribution is 126.8 L/m². The AUC during a dosing interval at steady state is 188 ng/mL. Omacetaxine is hydrolyzed by plasma esterases to the inactive metabolites 4'-demethyl-homoharringtonine (4'-DMHHT) and cephalotaxine with minimal hepatic metabolism. Urinary excretion of unchanged omacetaxine accounted for 12% to 15% of the dose as unchanged drug.²²

Selected therapeutic regimens of omacetaxine appear in Table 2.

PREPARATION

- A. Use omacetaxine powder for injection.
- B. Dilute with 0.9% sodium chloride injection (NS) to a concentration of 3.5 mg/mL.
- C. Dispense in a syringe.

Table 2. Selected therapeutic regimens of omacetaxine

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
1.25 mg/m ² bid ^a	SC	1 through 14	28 days (induction)	35 mg/m ²	22-29
1.25 mg/m ² bid ^a	SC	1 through 7	28 days (maintenance)	17.5 mg/m ²	22-30
Homoharringtonine trials					
0.2 to 3.75 mg/m ²	CIVI	1 through 5	—	1 to 18.75 mg/m ²	31
1 mg/m ²	IM	1 and 8	Monthly	2 mg/m ²	32
1.5 mg/m ²	CIVI	For 7 to 11 days after WBC <20x10 ⁹ /L (induction)	Monthly	—	33
1.5 mg/m ²	CIVI	1 through 7 or 9	Monthly	10.5 mg/m ² (13.5 mg/m ²)	33
2 mg/m ²	CIVI	1	Induction	2 mg/m ²	30
2 mg/m ² bid	SC	2 through 14, then		52 mg/m ²	
1.25 mg/m ² bid	SC	1 through 14		35 mg/m ²	
2.5 mg/m ²	CIVI	1 through 14	Monthly (induction)	35 mg/m ²	34,35
2.5 mg/m ²	CIVI	1 through 7	Monthly (maintenance)	17.5 mg/m ²	34,35
2-3 mg/m ²	CIVI	1 through 3	—	6-9 mg/m ²	36
2 – 8 mg/m ²	IV	1 through 5	—	10 – 40 mg/m ²	37
3 mg/m ²	CIVI	1 through 7	—	21 mg/m ²	36
5 mg/m ²	SC	1 through 9	—	45 mg/m ²	38-40
7 mg/m ²	CIVI	1 through 10	21 days	70 mg/m ²	41

Note: CIVI = continuous (24 hour) intravenous infusion; IM = intramuscular; IV = intravenous; SC = subcutaneous.

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

STABILITY

- Reconstituted omacetaxine solution is stable for 12 hours at room temperature or 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F).
- The reconstituted vial should be protected from light.

ADMINISTRATION

Omacetaxine is administered as a subcutaneous injection twice daily.

TOXICITIES

- Central Nervous System:** Headaches 18% to 36%.^{23,25,26}
- Constitutional:** Fatigue 18% to 45%,^{24,25,27} (grade 3 or 4) 3% to 9%²⁴⁻²⁶; pyrexia 23% to 29%,^{24,25} (grade 3 or 4) 2%²⁴; asthenia 17% to 27%^{24,25}; peripheral edema 13%,²⁴ (grade 3 or 4) 5% to 9%.²⁶
- Dermatologic:** Alopecia 18%,²⁴ rash 11%.²⁴
- Gastrointestinal:** Diarrhea 32% to 45%,²⁴⁻²⁶ (grade 3 or 4) 2%²³; constipation 18%²³; nausea 26% to 64%,²⁴⁻²⁴ (grade 3 or 4) 2%²⁴; vomiting 17%²⁵; abdominal pain 16%.²⁴

- Hematologic:** Anemia 22% to 100%,^{24,25,27} (grade 3 or 4) 22% to 39%^{24-27,29}; febrile neutropenia 7% to 12%^{26,29}; neutropenia 22% to 54%,²⁴⁻²⁷ (grade 3 or 4) 22% to 47%^{24-27,31}; thrombocytopenia 56% to 82%,²⁴⁻²⁸ (grade 3 or 4) 43% to 76%²⁴⁻²⁸; lymphopenia 18%,²⁵ (grade 3 or 4) 16%.²⁴
- Infection:** Bacterial, viral, fungal, and non-specified 42%,²⁴ (grade 3 or 4) 2% to 14%.^{24,26,29}
- Musculoskeletal:** Arthralgia 23%,²⁴ (grade 3 or 4) 2%²⁴; back pain 11%,²⁴ (grade 3 or 4) 2%²⁶; pain in extremity 11%.²⁴
- Pulmonary:** Cough 18%²⁴; epistaxis 15%,²⁴ (grade 3 or 4) 2%.²⁴

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