Cancer Chemotherapy Update

Drug Monographs: Bosutinib and Regorafenib

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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: Bosutinib

Synonyms: Bosulif; SKI-606

MECHANISM OF ACTION

Bosutinib is a dual Src/Abl tyrosine kinase inhibitor that selectively targets Src and Abl kinases. It has minimal activity against stem cell factor receptor (c-KIT) or platelet-derived growth factor receptor (PDGFR).¹⁻⁸

PHARMACOKINETICS

Following oral administration of a 500 mg dose, bosutinib has a maximum serum concentration (C_{max}) of 101.9 ng/mL to 114 ng/mL,^{1,3} a time to C_{max} (T_{max}) of 5 to 6 hours,^{1,3} and an area under the time versus concentration curve (AUC) of 2,064 ng•h/mL to 2,330 ng•h/mL.^{1,3} The C_{max} and AUC increase 1.8- and 1.7-fold, respectively, when the drug is given with a high-fat meal.⁸ Bosutinib has a volume of distribution (V_d) of 6,000 to 11,100 L, and a half-life ($t_{1/2}$) of 13 hours to 22.27 hours.^{1,3,4,8} Bosutinib is metabolized in the liver, primarily by the CYP3A4 enzyme. Bosutinib's metabolites are inactive, with oxydechlorinated bosutinib (19%) and N-desmethylated bosutinib (25%) being the major metabolites. Bosutinib N-oxide is a minor metabolite. Bosutinib excretion is primarily hepatic (93%), with about 3% of the drug excreted in the urine.⁸

Selected therapeutic regimens of bosutinib appear in Table 1.

PREPARATION

- A. Follow institutional policies for preparation of hazardous medications when dispensing bosutinib.

- B. Bosutinib is available as 100 mg and 500 mg tablets.

STORAGE

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

ADMINISTRATION

- A. Bosutinib is taken orally once a day.
- B. Bosutinib should be taken with food.

TOXICITIES

- A. Cardiovascular: Edema 4% to 15%,^{1,4,7,14} (grade 3 or 4) <1%^{1,7,14}; pleural or pericardial effusions 8%.¹⁵
- B. Central Nervous System: Dizziness 17% to 67%²; headache 10% to 25%,^{1,2,4,7,13} (grade 3 or 4) 1% to 3%.^{4,7,13}
- C. Constitutional: Arthralgia 12% to 14%,^{1,4} (grade 3 or 4) <1%^{1,4}; back pain 10% to 12%,^{1,4} (grade 3 or 4) 4%⁴; bone pain 4%⁷; fatigue 10% to 38%,^{1,2,4,5,7,9,11-13} (grade 3 or 4) 1% to 8%^{1,4,5,7,13}; muscle cramps 2%⁷; pyrexia 16% to 21%,^{1,7} (grade 3 or 4) <1% to 1%^{1,7}; weight loss 11%.⁴
- D. Dermatologic: Rash 14% to 44%,^{1,4,5,7,9,11-13} (grade 3 or 4) 1% to 13%.^{1,5,7,10,11,13}
- E. Gastrointestinal: Abdominal pain 9% to 23%,^{1,4,5,7,13} (grade 3 or 4) 1%^{1,4,7,13}; anorexia 13% to 38%,^{1,4,5} (grade 3 or 4) 1%^{1,5}; constipation 11%, (grade 3 or 4) <1%¹; diarrhea 17% to 93%,^{1,2,4,5,7,9-15} (grade 3 or 4) 6% to 23%^{1,4,5,7,9-15}; flatulence 7% to 31%⁵; nausea 17% to 79%,^{1,2,4,5,7,9-13,15} (grade

Table 1. Selected therapeutic regimens of bosutinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month	References
400 mg	PO	Daily	–	12,000 mg	2,4,5,11,12
500 mg ^a	PO	Daily	–	15,000 mg	1,3,5-10,13-16
600 mg ^a	PO	Daily	–	18,000 mg	2,5,8

Note: PO = oral.

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

- 3 or 4) 1% to 8%^{1,4,5,7,12,13}; vomiting 32% to 57%,^{1,4,5,7,9-13,15} (grade 3 or 4) 1% to 8%.^{1,4,5,7,9,11,13}
- F. Hematologic: Anemia 81% to 90%,^{1,6,7} (grade 3 or 4) 6% to 37%^{1,6,7,9,10,14,15}; neutropenia 28% to 46%,^{1,6,7} (grade 3 or 4) 10% to 46%^{1,6,7,9,10,13-15}; thrombocytopenia 58% to 66%,^{1,6,7} (grade 3 or 4) 14% to 65%.^{1,6,7,9,10,13-15}
- G. Hepatic: Elevated alkaline phosphatase 35%⁶; elevated alanine aminotransferase (ALT) 11% to 69%,^{1,5-7,11} (grade 3 or 4) 5% to 29%^{1,5-7,9-12,15}; elevated aspartate aminotransferase (AST) 13% to 59%,^{1,5-7,12} (grade 3 or 4) 2% to 19%.^{1,5-7,11,15}
- H. Infections: Pneumonia 6%⁹; upper respiratory infection 10%⁷; unspecified infections 49% to 56%,¹⁴ (grade 3 or 4) 10% to 15%.¹⁴
- I. Metabolic: Decreased bicarbonate 31%,⁶ hyperglycemia 31%,⁶ (grade 3 or 4) 1%⁶; hyperkalemia 23%⁶; hypermagnesemia 25% to 29%,^{1,6} (grade 3 or 4) 12%^{1,6,13}; hyperuricemia 42%, (grade 3 or 4) 6%¹; hypocalcemia 37% to 40%,^{1,6} (grade 3 or 4) 3% to 5%^{1,6}; hypomagnesemia 25% to 29%,^{1,6} (grade 3 or 4) 12%^{1,6}; hypophosphatemia 31% to 44%,^{1,6,7} (grade 3 or 4) 2% to 14%^{1,6,7}; increased lipase 24% to 38%,^{1,6,7} (grade 3 or 4) 7% to 9%.^{1,6,7}
- J. Neurologic: Asthenia 19%, (grade 3 or 4) 6%.⁴
- K. Renal: Increased creatinine 42%,⁶ (grade 3 or 4) 1%.⁶
- L. Respiratory: Cough 11% to 16%^{1,4}; dyspnea 11% to 25%,^{4,11} (grade 3 or 4) 5%⁹; nasopharyngitis 10%.¹

Name: Regorafenib

Synonyms: BAY 73-4506, *Stivarga*

MECHANISM OF ACTION

Regorafenib is a tyrosine kinase and vascular endothelial growth factor (VEGF) inhibitor. It inhibits tumor growth, angiogenesis, and metastasis by targeting

a variety of kinases involved in oncogenes, tumor angiogenesis, and maintenance of the tumor micro-environment. Regorafenib's targets include VEGF receptors 1-3, KIT, PDGFR- α , PDGFR- β , RET, FGFR, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, SAPK2, PTK5, and Abl.¹⁷⁻¹⁹

PHARMACOKINETICS

Regorafenib is 69% bioavailable from the oral tablet; an oral solution is reported to have a bioavailability of 83%.²⁰ A high-fat meal increases the mean AUC of the parent drug by 48% and decreases the mean AUC of the N-oxide and N-desmethyl metabolites by 20% and 51%, respectively. A low-fat meal increases the mean AUC of regorafenib and the N-oxide and N-desmethyl metabolites 36%, 40%, and 23%, respectively. Regorafenib has a maximum serum concentration (C_{max}) of 2.5 to 3.45 ng/mL,^{17,20} a T_{max} of 1 to 6 hours,^{18,20} and an AUC of 50.26 ng•h/mL to 70 ng•h/mL.^{17,20} Regorafenib is highly (99.5%) protein bound and has a half-life ($t_{1/2}$) of 20 to 40 hours.^{18,20}

Regorafenib is metabolized in the liver by CYP3A4 and UGT1A9 to 2 active metabolites: N-oxide-regorafenib and N-desmethyl-regorafenib.²⁰ Regorafenib is excreted primarily in the feces, with 47% as unchanged drug and 24% as the metabolites. About 19% is excreted renally, 17% as metabolites.²⁰ The elimination half life ($t_{1/2}$) is 28 hours.

Selected therapeutic regimens of regorafenib appear in Table 2.

PREPARATION

- Follow institutional policies for preparation of hazardous medications when dispensing regorafenib.
- Regorafenib is available as 40 mg tablets.

STORAGE

- 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.

Table 2. Selected therapeutic regimens of regorafenib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
160 mg ^a	PO	1 through 21	28 days	3,360 mg	17-20,24-28
160 mg	PO	4 through 10 18 through 24	28 days	2,240 mg	23
140 mg	PO	1 through 21	28 days	2,940 mg	21
120 mg	PO	1 through 21	28 days	2,520 mg	22
100 mg	PO	1 through 21	28 days	2,100 mg	22

Note: PO = oral.

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

ADMINISTRATION

- A. Regorafenib is taken orally once a day.
- B. The manufacturer recommends regorafenib be taken with a low-fat (<30%) breakfast.

TOXICITIES

- A. Cardiovascular: Hypertension 18% to 50%,^{17,18} (grade 3) 29% to 36%,^{19,24} (grade 3 or 4) 7% to 28%^{17,18,26-28}; unspecified thrombotic event (grade 4) 3%.^{19,24}
- B. Constitutional: Fatigue 17% to 50%,^{17,18,21} (grade 1 or 2) 32%,²¹ (grade 3) 6%,¹⁹ (grade 3 or 4) 10% to 15%^{17,26,28}; extremity pain 29%,²¹ (grade 1) 30%,²² (grade 3) 5%²¹; muscle pain 18%¹⁷; weight loss 13%.¹⁷
- C. Dermatologic: Alopecia 11% to 33%^{17,18}; dry skin 18%¹⁷; rash, desquamation 29% to 50%,^{17,18,21} (grade 1 or 2) 26%,²² (grade 3) 3%,²¹ (grade 3 or 4) 5% to 8%^{17,18,28}; rash, unspecified type (grade 3) 9%¹⁹; unspecified reaction 68%,¹⁷ (grade 3 or 4) 34%.¹⁷
- D. Gastrointestinal: Anorexia 24% to 50%,^{17,18} (grade 3) 6%,¹⁹ (grade 3 or 4) 8%¹⁸; diarrhea 21% to 60%,^{17,18,21,23} (grade 3) 3%,²¹ (grade 3 or 4) 3% to 18%^{17,18,23,26-28}; mucositis 18% to 40%,^{17,18,23} (grade 1 or 2) 24%,²¹ (grade 3 or 4) 8%^{18,23}; nausea 25% to 40%,²³ (grade 3 or 4) 4%²³; xerostomia 16%,¹⁷ (grade 3 or 4) 3%.¹⁷
- E. Hematologic: Leukopenia 32% to 40%,²³ (grade 3 or 4) 8% to 15%²³; neutropenia 40% to 50%,²³ (grade 3 or 4) 28% to 40%²³; thrombocytopenia 11%,¹⁷ (grade 3 or 4) 3%.¹⁷
- F. Hepatic: Hyperbilirubinemia (grade 3 or 4) 8%.²⁶
- G. Metabolic/Endocrine: Elevated lipase (grade 3) 6%¹⁹; hyperuricemia (grade 4) 3% to 6%^{19,24}; hypophosphatemia (grade 3) 14% to 15%^{19,24}; hypothyroidism (grade 1 or 2) 26%.²²

H. Neurologic: Hand-foot syndrome 32% to 67%,^{17,18,21-23} (grade 3) 4% to 25%,^{19,21-24,26} (grade 3 or 4) 17% to 32%^{17,18,26,28}; unspecified neurologic toxicity 20% to 44%,²³ (grade 3 or 4) 4%²³; voice changes 34% to 42%,¹⁸ (grade 3 or 4) 3%.¹⁷

I. Otic: Unspecified reaction 11%.¹⁷

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