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Cancer Chemotherapy Update

Drug Monographs: Dabrafenib and Trametinib

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: Dabrafenib

Synonyms: Tafinlar, GSK2118436

MECHANISM OF ACTION

Dabrafenib is a selective kinase inhibitor that is active against several mutated forms of BRAF kinase including BRAF V600E, BRAF V600K, and BRAF V600D.[1] BRAF kinases are part of the mitogen-activated protein kinase (MAPK) pathway, which promotes cellular proliferation. Oncogenic mutations leading to activation of BRAF occur in a variety of tumor types, including cutaneous melanoma (50% of cases), papillary thyroid cancer (46% of cases), borderline ovarian tumors (34% of cases), and hairy cell leukemia (100% of cases).[2] In cutaneous melanoma, the activating mutation in the BRAF gene is V600E in 70% to 95% of cases and V600K in 5% to 30% of cases. Mutant BRAF predicts a poor prognosis in metastatic melanoma.[3]

PHARMACOKINETICS

Following oral administration of 150 mg every 12 hours, the median time to peak plasma concentration (T_{max}) is 2 hours[1,2,4] and the mean absolute bioavailability is 95%.[1] The geometric mean area under the plasma concentration-time curve (AUC) is 2619 ng•h/mL; the mean maximum plasma concentration (C_{max}) is 806 ng/mL.[2] Administration of dabrafenib with a high-fat meal causes a decrease in C_{max} of 51%, a decrease in AUC of 31%, and an increase in T_{max} to 3.6 hours compared to fasting state administration.[1] Dabrafenib is 99.7% protein bound, with an apparent volume of distribution (V_d) of 70.3 L. Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4 to hydroxy-dabrafenib, probably an active metabolite, which is further oxidized by CYP3A4 to carboxy-dabrafenib, which is eliminated in bile and urine.[1] The mean terminal half life ($t_{\frac{1}{2}}$) is 5.2 to 8 hours,[1,2] and the apparent clearance (CL) is 17 L/h following 14 days of twice-daily dosing.[1] Radioactive dose testing reveals that 71% of dabrafenib is eliminated in the feces and 23% in the urine.[1]

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

PREPARATION

A. Follow institutional policies for preparation of hazardous medications when dispensing dabrafenib.
B. Dabrafenib is available as 50 mg and 75 mg capsules.

STORAGE

A. Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).
B. Brief (less than 24 hours) exposure to temperatures up to 30°C (86°F) is acceptable.

ADMINISTRATION

A. Dabrafenib is taken orally, with the daily dose divided and given twice a day.
B. Dabrafenib should be taken 1 hour before or 2 hours after food.

Table 1. Selected therapeutic regimens of dabrafenib

Dose	Route of administration	Administered	Cycle length	Total dose/month	References
75 mg	PO	Twice daily	–	4,500 mg	4
150 mg[a]	PO	Twice daily	–	9,000 mg	1-5
200 mg	PO	Twice daily	–	12,000 mg	2
300 mg	PO	Twice daily	–	18,000 mg	2

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

TOXICITIES

A. Cardiovascular: Hypertension (grade 1 or 2) 4%[4]; intracranial hemorrhage (all grades) 6%,[3] (grade 4) 0.5%[3]; peripheral edema (grade 1 or 2) 17%.[4]

B. Constitutional: Asthenia (grade 2) 3%,[5] chills (grade 1 or 2) 17%,[4] (grade 2) 2%,[3] (grade 3) 0.5%[3]; fatigue (grade 1 or 2) 34%,[4] (grade 2) 5% to 7%,[2,3,5] (grade 3) 0.5% to 1%,[2,3,5] (grade 3 or 4) 6%[4]; night sweats (grade 1 or 2) 6%[4]; pyrexia (all grades) 26%,[3] (grade 1 or 2) 26%,[4] (grade 2) 5% to 9%,[2,3,5] (grade 3) 0.5% to 3%.[2,3,5]

C. Dermatologic: Acneiform dermatitis (grade 1 or 2) 4%[4]; actinic keratosis (all grades) 5% to 10%,[2,3] (grade 1) 9%,[2] (grade 2 or above) 0.5%[2]; alopecia (grade 1 or 2) 34%,[4] (grade 2) 1%[3]; cutaneous basal cell carcinoma (all grades) 2%[3,5]; cutaneous squamous cell carcinoma (grade 1 or 2) 2%,[4] (grade 2) 2%,[5] (grade 3) 4% to 17%[2-5]; hyperkeratosis (grade 1) 23%,[2] (grade 1 or 2) 30%,[4] (grade 2) 8% to 12%,[3,5] (grade 2 or above) 3%,[2] (grade 3) 0.5%,[3,5] (grade 4) 0.5%[5]; keratocanthoma (all grades) 1% to 2%[2,3]; melanocytic nevus (grade 2) 0.5%[3]; mycosis fungoides (grade 1) 0.5%[5]; new primary malignant melanoma (all grades) 1%[5]; palmar plantar erythrodysesthesia or hyperkeratosis (grade 2) 5% to 6%,[3,5] (grade 3) 2%[3,5]; papilloma (grade 1 or 2) 15%[4]; rash (grade 1 or 2) 36%,[4] (grade 2) 3%[3]; phototoxic reaction (grade 1) 2%,[5] (grade 2) 1%.[5]

D. Gastrointestinal: Constipation (grade 1 or 2) 11%[4]; decreased appetite (grade 1 or 2) 19%,[4] (grade 2) 2%,[3] (grade 3) 1%[3]; diarrhea (grade 1 or 2) 28%,[4] (grade 2) 1%,[3] (grade 3) 0.5%[3]; nausea (grade 1 or 2) 21%,[4] (grade 2) 1% to 2%,[3,5] (grade 3) 0.5%[3]; vomiting (grade 1 or 2) 15%,[4] (grade 2) 1% to 3%.[3,5]

E. Hematologic: Agranulocytosis (grade 4) 0.5%[3]; neutopenia (grade 3) 0.5%,[5] (grade 4) 0.5%[3]; thrombocytopenia (grade 3) 0.5%.[5]

F. Hepatic: Alkaline phosphatase increase (grade 1 or 2) 2%[4]; alanine aminotransferase (ALT) increase (grade 2) 2%,[3] (grade 3) 1%.[3]

G. Metabolic: Amylase increase (grade 4) 0.5%,[3] lipase increase (grade 4) 0.5%.[3]

H. Musculoskeletal: Arthralgia (grade 1 or 2) 34%,[4] (grade 2) 2% to 5%,[3,5] (grade 2 or higher) 5%,[2] (grade 3) 0.5%[5]; myalgia (grade 1 or 2) 21%,[4] (grade 2) 2%,[3] (grade 3 or 4) 2%.[4]

I. Neurologic: Convulsion (grade 4) 0.5%[3]; headache (grade 1 or 2) 28%,[4] (grade 2) 4% to 5%,[3,5] (grade 3) 0.5%,[3] pain in extremity (grade 2) 1%.[3]

J. Respiratory: Cough (grade 1 or 2) 21%.[4]

Name: Trametinib
Synonyms: Mekinist, GSK1120212

MECHANISM OF ACTION

Trametinib reversibly and selectively inhibits the activation of mitogen-activated extracellular signal regulated kinase (MEK) 1 and MEK2 and inhibits their kinase activity.[6,7] MEK1 and MEK2 are downstream from BRAF in the MAPK pathway.[6]

PHARMACOKINETICS

Trametinib has a T_{max} of 1.5 hours[6,8] and a mean absolute bioavailability of 72% following a single 2 mg oral dose.[6] With 2 mg once-daily dosing, the mean C_{max} is 22.2 ng/mL and AUC is 370 ng•h/mL.[8] Administration of trametinib with a high-fat meal decreased AUC by 24% and C_{max} by 70% and prolonged T_{max} out to 5.5 hours compared to fasting state administration.[6] Trametinib is 97% protein bound and has an apparent V_d of 214 L.[6] Metabolism is primarily by deacetylation, monooxygenation, and glucuronidation, with 80% of a radioactive dose recovered in the feces and less than 20% recovered in the urine.[6] $T_{\frac{1}{2}}$ is 3.8 to 4.8 days, and CL is 4.9 L/h.[6,8] Selected therapeutic regimens of trametinib appear in **Table 2.**

PREPARATION

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

Table 2. Selected therapeutic regimens of trametinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month	References
2 mg[a]	PO	Daily	–	60 mg	6,7,9,10
2.5 mg	PO	Daily	–	75 mg	8
3 mg	PO	Daily	–	90 mg	8

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

B. Trametinib is available as 0.5, 1, and 2 mg tablets.
C. The product labeling states trametinib be dispensed in the original bottle without removing the desiccant. The labeling provides no explanation for this requirement.

STORAGE

A. Store refrigerated at 2°C to 8°C (36°F to 46°F).
B. Brief (less than 24 hours) exposure to temperatures up to 30°C (86°F) is acceptable.

ADMINISTRATION

A. Trametinib is taken orally once a day.
B. Trametinib should be taken on an empty stomach (1 hour before or 2 hours after food).

TOXICITIES

A. Cardiovascular: Hypertension (all grades) 15%,[9] (grade 1 or 2) 6%,[10] (grade 2) 3%,[9] (grade 3) 12%[9]; left ventricular dysfunction or decrease in ejection fraction (all grades) 7% to 8%,[8,9] (grade 1) 2% to 3%,[7,8] (grade 2) 4%,[7,8] (grade 3) 1%[8]; left ventricular ejection fraction reduction (grade 3) 3%[10]; peripheral edema (all grades) 26% to 35%,[7-10] (grade 1) 23% to 31%,[7,8] (grade 2) 4% to 6%,[7-9] (grade 3) 0.5% to 3%[8-10]; pulmonary embolism (grade 4) 1%[10]; pulmonary hypertension (grade 3) 1%[7]; serious cardiac-related events causing permanent discontinuation of trametinib (grade 3) 1%.[9]

B. Constitutional: Fatigue (all grades) 26% to 35%,[7-10] (grade 1) 18% to 19%,[7,8] (grade 2) 5% to 12%,[7-9] (grade 3) 2% to 4%.[7-10]

C. Dermatologic: Acneiform dermatitis (all grades) 19%,[9] (grade 2) 9%,[9] (grade 3) 1%[9]; alopecia (all grades) 17%,[9] (grade 2) 1%,[9] (grade 3) 0.5%[9]; dry skin (grade 1 or 2) 22%[10]; dry skin, chapped skin, or skin fissures (all grades) 18% to 31%,[7,8] (grade 1) 15% to 23%,[7,8] (grade 2) 3% to 8%[7,8]; pruritis (all grades) 14% to 27%,[7,8,10] (grade 1) 9% to 15%,[7,8] (grade 2) 5%,[8] (grade 3) 1%[10]; rash (all grades) 57%,[9] (grade 2) 19%,[9] (grade 3) 3%,[9] (grade 4) 0.5% to 1%[7,9]; rash or acneiform dermatitis (all grades) 75% to 85%,[7,8,10] (grade 1) 38% to 39%,[7,8] (grade 2) 33% to 38%,[7,8] (grade 3) 7% to 9%,[7,8,10] (grade 4) 0.5%.[8]

D. Gastrointestinal: Constipation (all grades) 5% to 14%,[8-10] (grade 1) 4%,[8] (grade 2) 1%,[8,9] (grade 1 or 2) 14%[10]; decreased appetite (all grades) 10% to 11%,[8,10] (grade 1) 7%,[8] (grade 2) 2%,[8] (grade 3) 0.5% to 1%[8,10]; diarrhea (all grades) 42% to 52%,[7-10] (grade 1) 31% to 35%,[7,8] (grade 2) 6% to 11%,[7-9] (grade 3) 1% to 4%,[8,10] (grade 4) 0.5%[9]; dry mouth (all grades) 5% to 11%,[8,10] (grade 1) 5%,[8] (grade 1 or 2) 11%[10]; mucosal inflammation (all grades) 4% to 7%,[7,8] (grade 1) 4% to 5%,[7,8] (grade 2) 2%[8]; nausea (all grades) 12% to 30%,[7-10] (grade 1) 12% to 22%,[7,8] (grade 2) 2% to 5%,[8,9] (grade 3) 1%[9]; vomiting (all grades) 8% to 18%,[7-10] (grade 1) 8% to 11%,[7,8] (grade 2) 1% to 5%,[8,9] (grade 1 or 2) 18%,[10] (grade 3) 0.5% to 1%.[8,9]

E. Hematologic: Thrombocytopenia (all grades) 5%,[8] (grade 1) 4%,[8] (grade 2) 0.5%,[8] (grade 3) 0.5%,[8] (grade 4) 0.5% to 1%.[7,8]

F. Hepatic: Aminotransferase increase (grade 3) 2%.[10]

G. Neurologic: Abdominal pain (grade 1 or 2) 15%.[10]

H. Ocular: Blurred vision (grade 1) 2%,[7] (grade 1 or 2) 4%[9]; central serous retinopathy (all grades) 2%[10]; dry eyes (grade 1) 2%[7]; ocular toxic effects (any) (all grades) 9% to 15%,[8,9] (grade 1) 13%,[8] (grade 2) 2%,[8] (grade 3) 0.5%[8]; periorbital edema (all grades) 5%,[8] (grade 1) 5%,[8] (grade 2) 0.5%[8]; reversible chorioretinopathy (grade 3) 0.5%[9]; visual impairment (grade 1) 4%.[7]

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