The Pharmacist Activist

Volume 8, No. 12 • December 2013

Editorial

May the Blessings of Christmas Continue into a Healthy and Enjoyable New Year!

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New Drug Review

Dabrafenib mesylate
(Tafinlar – GlaxoSmithKline)

Antineoplastic Agent

New Drug Comparison Rating (NDCR) = 4

(significant advantage[s]) in a scale of 1 to 5 with 5 being the highest rating

Indication:
Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Comparable drug:
Vemurafenib (Zelboraf).

Advantages:
- Was evaluated in patients with brain metastases (whereas such patients were not included in studies with vemurafenib);
- May be less likely to cause new non-cutaneous squamous cell carcinomas;
- May be less likely to cause photosensitivity reactions and severe dermatologic reactions;
- May be less likely to cause hepatic adverse events;
- May be less likely to cause prolongation of the QT interval and related adverse events/interactions.

Disadvantages:
- May be more likely to cause serious febrile reactions;
- May be more likely to cause hyperglycemia;
- May reduce effectiveness of hormonal contraceptives;
- May interact with more medications.

Most important risks/adverse events:
New primary cutaneous malignancies (dermatologic evaluations should be performed before initiating therapy, every 2 months during therapy, and for up to 6 months following discontinuation of treatment); tumor promotion in BRAF wild-type melanoma; serious febrile drug reactions (withhold treatment if fever is 101.3°F or higher, or complicated fever occurs); hyperglycemia; uveitis and iritis; potential risk of hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency; may cause harm to a fetus and is classified in Pregnancy Category D (may decrease effectiveness of hormonal contraceptives and an alternative method of contraception should be used; non-hormonal contraception should be used during treatment and for 4 weeks after treatment is discontinued); potential risk for impaired spermatogenesis; is a substrate of CYP3A4 and CYP2C8 and concurrent use of strong inhibitors (e.g., clarithromycin, gemfibrozil) or strong inducers (e.g., rifampin) of these pathways is not recommended; action may be reduced by drugs that increase gastric pH (e.g., omeprazole).

Most common adverse events:
Hyperkeratosis (37%), headache (32%), fever (28%), arthralgia (27%), papilloma (27%), alopecia (22%), palmar-plantar erythrodysesthesia syndrome (20%).

Usual dosage:
150 mg twice a day at least 1 hour before or at least 2 hours after a meal; product labeling should be consulted for recommendations of dosage adjustments when adverse events are experienced.

Products:
Capsules - 50 mg, 75 mg.

Comments:
A protein designated as BRAF is an important component of a pathway involved in normal cell growth and survival. Mutations that keep the BRAF protein in an active state may cause excessive signaling in the pathway, resulting in uncontrolled cell growth. These mutations, most often BRAF V600 mutations, occur in approximately one-half of melanomas, with an estimated 85% being of the V600E type and 10% of the V600K type. Dabrafenib is an inhibitor of some mutated forms of BRAF kinases, including V600E, and its properties and use are most similar to those of vemurafenib that was first marketed in 2011.

The effectiveness of dabrafenib was demonstrated in a study in which it was compared with dacarbazine and in which the main efficacy outcome measure was progression-free survival. The patients treated with dabrafenib had a delay in tumor growth that was 2.4 months later than those receiving dacarbazine (5.1 vs. 2.7 months). Dabrafenib was also evaluated in patients with brain metastases and the overall intracranial response rate (OIRR) was 18%, and the median duration of the OIRR was 4.6 months.

Daniel A. Hussar

New Drug Review

Trametinib dimethyl sulfoxide (Mekinist – GlaxoSmithKline)

Antineoplastic Agent

New Drug Comparison Rating (NDCR) = 4

(significant advantage[s]) in a scale of 1 to 5 with 5 being the highest rating

Indication:

Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.

Comparable drug:

Vemurafenib (Zelboraf).

Advantages:

- Has a unique mechanism of action (inhibits mitogen-activated extracellular signal-regulated kinase [MEK] pathways);
- Has activity against BRAF V600K mutation;
- May be less likely to cause new non-cutaneous squamous cell carcinomas;
- May be less likely to cause photosensitivity reactions and hepatic adverse events;
- May be less likely to cause prolongation of the QT interval and related adverse events/interactions;
- Is administered once a day (whereas vemurafenib is administered twice a day);
- Less likely to interact with other drugs.

Disadvantages:

- May be more likely to cause cardiomyopathy;
- May be more likely to cause dermatologic toxicity;
- May be more likely to cause retinal pigment epithelial detachment and retinal vein occlusion;
- May be more likely to cause interstitial lung disease.

Most important risks/adverse events:

Cardiomyopathy (e.g., cardiac failure, left ventricular dysfunction, decreased left ventricular ejection fraction [LVEF]; LVEF should be assessed before treatment, 1 month following initiation of treatment, and at 2- to 3-month intervals during treatment); serious skin toxicity (should monitor for toxicities and secondary infections); interstitial lung disease; retinal pigment epithelial detachment; retinal vein occlusion; may cause harm to a fetus and is classified in Pregnancy Category D (women of childbearing potential should use contraception during treatment and for 4 months following discontinuation of treatment); may impair fertility in female patients.

Most common adverse events:

Rash (57%), diarrhea (43%), lymphedema (32%), dermatitis acneiform (19%), hypertension (15%), stomatitis (15%), hemorrhage (13%), abdominal pain (13%).

Usual dosage:

2 mg once a day at least 1 hour before or at least 2 hours after a meal; product labeling should be consulted for recommendations of dosage adjustments when adverse events are experienced.

Products:

Tablets - 0.5 mg, 1 mg, 2 mg.

Comments:

A protein designated as BRAF is an important component of a pathway involved in normal cell growth and survival. Mutations that keep the BRAF protein in an active state may cause excessive signaling in the pathway, resulting in uncontrolled cell growth. Vemurafenib and dabrafenib inhibit some mutated forms of BRAF kinases (V600E). However, the benefit from these agents may be of brief duration because of resistance involving mitogen-activated extracellular signal-regulated kinase (MEK) pathways. MEKs are upstream regulators of the extracellular signal-related kinase pathway which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2. Trametinib is a kinase inhibitor that inhibits MEK1 and MEK2 activation and activity, and is the first drug with this mechanism of action.

The effectiveness of trametinib was demonstrated in a study in which patients received either trametinib or chemotherapy (dacarbazine or paclitaxel). The primary efficacy outcome measure of the study was progression-free survival. Patients treated with trametinib had a delay in tumor growth that was 3.3 months later than those receiving dacarbazine or paclitaxel (4.8 vs. 1.5 months). Trametinib has been initially approved for use as a single agent but investigational studies of its use in combination with dabrafenib have demonstrated significantly greater response rates, progression-free survival, and duration of response compared with dabrafenib monotherapy.

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**All issues of The Pharmacist Activist are available without charge at www.pharmacistactivist.com.*

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