Drug Information Bulletin

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Volume: 07 ***Number: 44*** ***9th February 2014***

Content

Editorial

It has been noticed that the Ministry of Health and Family Welfare, Govt. of India has published an advertisement seeking application for the "National Florence Nightingale Nurses Award" to recognize meritorious services of Nurses working in the State, Central, Autonomous Institutions, Private, Missionary and Voluntary organization in India. This award is being given on 12th May every year to recognize the service of a Nurse in India, which will in turn encourage other Nurses. Similar award is given to recognize doctors on 1st July every year, which will encourage doctors to serve better the society. Though two important health providers are being recognized, very unfortunately the third important health providers –"Pharnacists" are ignored till date.

A few years back Her Excellency Mrs. Prativa Patil, President of India, in a programme at New Delhi declared that similar award will be given to the Pharmacist to recognize their contribution to the health care system. Very unfortunately that has not happened till date.

It may be due to bureaucratic delay or may be lack of persuasion by the pharmaceutical Organizations and Pharmacy Council of India.

It is high time that all pharmaceutical organizations be united and pursues the matter. The Pharmacy Council of India has extra responsibility in this matter being the highest authority of pharmacists. Hope we will see an similar advertisement seeking recommendation for such an award along with the next advertisement seeking recommendation for "Florence Nightingale Award" and "Dr. B.C.Roy Award".

Dr. Subhash C. Mandal
Editor

New Drug: Dabrafenib

Approved indication: metastatic melanoma
Taflinar (GlaxoSmithKline)
50 mg and 75 mg capsules
Australian Medicines Handbook section 14.2.4

Like vemurafenib (Aust Prescr 2012;35:128-35), dabrafenib is indicated for patients with inoperable or stage IV metastatic melanoma with a BRAF V600 mutation. These mutations are present in about half of people with melanomas. BRAF V600E accounts for most of

them (80–90%) with BRAF V600K being less common. The mutations result in expression of an abnormal protein kinase which continuously stimulates tumour cell growth. Dabrafenib is thought to slow the growth and spread of cancer cells by competitively inhibiting the abnormal BRAF kinase.

The approval of dabrafenib (150 mg orally twice daily) is based on a pivotal open-label comparative trial with dacarbazine (1000 mg/m^2 intravenously every three weeks). Only people with previously untreated BRAF V600E-positive melanoma and no active brain metastases were enrolled. Treatment was given until disease progressed, the patient died or adverse events were intolerable. Patients in the dacarbazine arm were allowed to cross over after confirmation of disease progression. More patients responded to dabrafenib than to dacarbazine and progression-free survival was significantly longer (see Table 1A).1

Dabrafenib has also been investigated in patients with brain metastases (1–4 lesions) but no neurological symptoms.2 There was no treatment comparator in the trial. Responses appeared to be better in patients with the BRAF V600E mutation compared to those with the V600K mutation. Response rates were similar regardless of whether the patient had received local treatment (brain surgery or radiotherapy) or not (see Table 1B).2

Table 1 **Efficacy of dabrafenib in BRAf V600-positive metastatic melanoma**

A Patients without brain metastases – phase III trial1

	dabrafenib	**dacarbazine**
Mutation	BRAF V600E (187 patients)	BRAF V600E (63 patients)
Response rate	50% (6 complete responses, 87 partial responses)	7% (1 complete response, 3 partial responses)
Median progression-free survival	5.1 months	2.7 months
12-month overall survival	70%	63%

B Patients with brain metastases – phase II trial2

dabrafenib				
Mutation	BRAF V600E		BRAF V600K	
Patients	untreated brain metastases (74 patients)	progressive brain metastases after local treatment (65 patients)	untreated brain metastases (15 patients)	progressive brain metastases after local treatment (18 patients)
Overall intracranial	39.2% (2 complete	30.8% (20 partial	6.7% (1 partial	22.2% (4 partial

response rate	responses, 27 partial responses)	responses)	response)	responses)
Median progression-free survival	3.7 months	3.8 months	1.9 months	3.6 months
Median overall survival	7.6 months	7.2 months	3.7 months	5.0 months

Adverse events with dabrafenib were more common in patients with brain metastases2 compared to those without brain lesions1 (82% vs 53% of patients), but discontinuations because of an event were similar (3% vs 2%). In a safety cohort of 187 patients, the most common adverse reactions were hyperkeratosis (37% of patients), headache (32%), fever (28%), arthralgia (27%), skin papilloma (24%), hair loss (22%), palmar–plantar erythrodysaesthesia (20%), fatigue (19%), nausea (19%), asthenia (18%), rash (17%), vomiting (12%), cough (12%), back pain (12%), constipation (11%) and diarrhoea (11%). Hypophosphataemia (37%) and increased alkaline phosphatase (19%) also occurred frequently.

Some patients (9%) developed cutaneous squamous cell carcinoma, often in the first 12 weeks of treatment. New primary melanomas were also reported so regular skin examination is recommended. Lesions should be excised and treatment can continue.

Uveitis and iritis have been reported with dabrafenib so vision should be monitored. Pancreatitis can occur and investigation of unexplained abdominal pain should include tests for serum lipase. Monitoring serum glucose is recommended for patients with diabetes or high blood sugar as hyperglycaemia was a problem in the trials. Treatment interruption is recommended if renal failure or fever develops.

Dabrafenib should be taken one hour before or two hours after a meal. If a dose is missed, it should not be taken within six hours of the next dose. Following oral administration, peak plasma concentrations of dabrafenib are reached after two hours. Its terminal half-life is eight hours and the dose is excreted in the faeces (71%) and urine (23%). Although there are no clinical data, dabrafenib exposure could potentially be increased in patients with moderate to severe hepatic impairment, and caution is urged.

Dabrafenib is metabolised by cytochrome P450 (CYP) 2C8 and 3A4 so inhibitors of these enzymes, such as ketoconazole and gemfibrozil, increase dabrafenib exposure. Potent CYP 2C8 inducers such as rifampicin, phenytoin and St John's wort should be avoided.

Dabrafenib induces UDP glucuronosyl transferase and numerous cytochrome enzymes (CYP3A4, 2C9, 2B6, 2C8 and 2C19) so it may lower serum concentrations of many drugs including midazolam, warfarin, hormonal contraceptives, dexamethasone and immunosuppressants. Drugs that increase gastric pH, such as proton pump inhibitors and H2 antagonists, could potentially reduce the bioavailability of dabrafenib.

Dabrafenib may prolong progression-free survival in patients with inoperable or metastatic melanoma. However, patients must have a confirmed BRAF V600 mutation before they can start treatment. It is not yet known how dabrafenib will compare to other treatments for this disease such as vemurafenib and ipilimumab.

REFERENCES

1. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic about this drug was available on the website of the melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-65.
2. Long GV, Trefzer U, Davis MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:1087-95 .

Source: *Aust Prescr 2014;37:28-35*

Palliative Care Formulary updated monographs (January 2014)

The online Palliative Care Formulary is being continually updated. The following monographs have been updated and supersede those in the publication of the 4th edition of the Palliative Care formulary (PCF4) and PCF4+ 2013 epdf. They can be accessed from the formulary section of the website.

Chapter 1: Rectal products for constipation, Pancreatin

Chapter 2: Glyceryl trinitrate, Systemic local anaesthetics Note: information relating to flecainide has been moved into systemic local anaesthetics monograph

Chapter 8: Methenamine hippurate, Tamsulosin

For a full list of all the monographs updated since the publication of PCF4, see:
http://www.palliativedrugs.com/download/PCF_updated_monographs_list_1401_final.pdf

Nomination Invited:

ANNUAL AWARDS OF SOCIETY FOR ETHNOPHARMACOLOGY KOLKATA, INDIA

Society for Ethnopharmacology, Kolkata, India (SFE), is registered under the West Bengal Society Registration act 1961 and affiliated to the International Society for Ethnopharmacology (UK). SFE, Kolkata,

To recognize the outstanding contribution in the area of medicinal pant research and Ethnopharmacology, the Society has instituted several awards. Nominations are invited for the following awards of the Society for Ethnopharmacology, Kolkata (SFE) which will be conferred during its First Congress at Sri Ramachandra University, Porur, Chennai during March 07-09, 2014.

NAME OF THE AWARDS:

- SFE Lifetime Achievement Award – 2014 (*"Bisheswar Saha Memorial Award")*
- SFE Outstanding Ethnopharmacologist Award -2014 (*"Harihar Mukherjee Memorial Award")*
- SFE Merit of Excellence Award – 2014
- SFE - Herbal industry leader award – 2014
- SFE - Best Entrepreneur Award – 2014
- SFE Outstanding Service Award – 2014
- SFE Best Poster Presentation Award – 2014 (*"Manjusree Pal Memorial Award")*
- SFE Best Oral Presentation Award – 2014
- SFE Travel Grant Award – 2014

Detail of nomination procedure, format is available in the SFE website: www.ethnopharmacology.in