New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Gefitinib

Iressa (AstraZeneca)

250 mg tablets

Approved indication: non-small cell lung cancer

Australian Medicines Handbook section 14.3

Growth factors have an important role in regulating cell proliferation. Abnormalities in the receptors for growth factors can result in cancer development. The epidermal growth factor receptor may be involved in transmitting cellular signals that lead to the progression of lung cancer. These signals can be blocked by inhibiting the enzyme tyrosine kinase.

Gefitinib is a tyrosine kinase inhibitor which can be taken by mouth. It has a bioavailability of 59%, but absorption is not altered by fasting. Gefitinib is metabolised by cytochrome P450 3A4 so it has the potential to interact with drugs that induce, or are metabolised by, this enzyme system. Interactions with itraconazole and rifampicin have been confirmed in volunteers. In clinical trials there have been interactions with metoprolol and possibly warfarin. As most of the drug is eliminated by liver metabolism and, as liver enzymes can increase during treatment, patients should have their liver function checked.

In an early clinical trial gefitinib was given to 71 patients with a variety of cancers that had not responded to other treatment. Although several patients dropped out of the trial, 26 completed at least three months of therapy. Only nine of the 39 patients with non-small cell lung cancer continued treatment for three months. The major dose-limiting toxicities were diarrhoea and rash.[1]

When used as monotherapy for previously-treated patients with locally advanced or metastatic non-small cell lung cancer gefitinib has produced a response in 9–19% of patients. Although treatment relieved some patients' symptoms, the median survival was only 6–8 months. When used in combination with other anticancer drugs in previously untreated patients gefitinib does not improve survival.

Most patients will suffer adverse effects from treatment. These include diarrhoea, rashes and other skin problems, nausea and vomiting. *Australian Prescriber's* sister journal in Japan, Kusuri-no-Check, has been concerned about deaths from gefitinib. Approximately 23 500 people have been treated in Japan, but the drug has been implicated in the deaths of 183.[2] Many of these deaths may have been the result of acute interstitial pneumonia.[3]

Although gefitinib has been marketed before the results of clinical trials have been published, its role in therapy will require further study. Its Australian approval restricts it to patients with locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy.

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2. Hama R, Sakaguchi K. The gefitinib story. ISDB Newsletter 2003;17:6-9.
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Voriconazole

Vfend (Pfizer)

50 mg and 200 mg tablets

30 mL glass vials containing 200 mg as lyophilised powder

Approved indication: systemic fungal infections

Australian Medicines Handbook section 5.2.3

The triazole antifungal drugs, such as fluconazole and itraconazole can be used to treat systemic fungal infections. Their fungicidal activity results from the inhibition of ergosterol synthesis in the cell membrane. Voriconazole is a new triazole drug with a broad spectrum of activity. In addition to the treatment of serious fungal infections, voriconazole can be used to prevent infections in patients with febrile neutropenia.

A clinical trial randomised 837 patients with febrile neutropenia to empirical therapy with liposomal amphotericin B or voriconazole. Fungal infections occurred in 21 patients given amphotericin B and in eight patients taking voriconazole. Breakthrough infections were particularly reduced in patients with relapsed leukaemia or an allogenic transplant.[1]

In a study of 277 patients with invasive aspergillosis 29% of those taking voriconazole had died within 12 weeks compared with 42% of those taking amphotericin B. Voriconazole can also be used when fungal infections such as invasive candidiasis do not respond to other antifungal drugs.

A loading dose of voriconazole will produce steady-state concentrations within 24 hours rather than the six days it usually takes with twice-daily doses. The tablets are well absorbed so the loading dose can be given orally. Voriconazole is metabolised in the liver and as this metabolism becomes saturated voriconazole has non-linear pharmacokinetics. There is a lot of variability in the pharmacokinetics of voriconazole, particularly in certain ethnic groups who are poor metabolisers. As the metabolism of voriconazole involves cytochrome P450 2C9, 2C19 and 3A4 there are many potential drug interactions.

Co-administration with drugs such as carbamazepine, ergotamine, pimozide and cisapride is contraindicated.

Hepatic toxicity including fatal liver failure can occur so patients need regular monitoring of liver function. A more common adverse reaction is altered vision. This affects approximately 30% of patients. They may complain of blurring, photophobia or changes in colour vision. Some will develop hallucinations. Rashes are common and some patients have developed Stevens-Johnson syndrome.

Although voriconazole has some significant adverse effects some of these, such as renal dysfunction, occurred less frequently than they did with amphotericin B. There is, however, controversy about whether voriconazole is as effective as amphotericin B. In the study of febrile neutropenia the overall treatment success rate was 26% for voriconazole and 30.6% for liposomal amphotericin B. The American Antiviral Drugs Advisory Committee recommended that the Food and Drug Administration should not approve voriconazole.[2] While there are problems with fluconazole and itraconazole, the role of voriconazole requires further study.

REFERENCES[†]

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2. Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever [letter]. N Engl J Med 2002;346:289-90.

[†] At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

Correction

New drugs (Aust Prescr 2003;26:46)

There was an error in the comment about fibrin sealant Tisseel Duo 500 (see letter page 76). The components of this new presentation of fibrin sealant are contained in preloaded syringes rather than vials. The product only needs to be thawed out before use, so the preparation time can be reduced by warming. After thawing, the product is viable for up to 48, not four, hours.

Answers to self-test questions

1. False
2. True
3. True
4. True
5. False
6. False
7. False
8. True

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Postal: Australian Prescriber Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 4633

Editorial office

For general correspondence such as letters to the Editor, please contact the Editor.

Telephone: (02) 6282 6755

Facsimile: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com