New drugs

Afatinib

Approved indication: non-small cell lung carcinoma
Giotrif (Boehringer Ingelheim)
10 mg, 30 mg, 40 mg and 50 mg film-coated tablets
Australian Medicines Handbook section 14.2.3

Like erlotinib (Aust Prescr 2006;29:53-5), gefitinib (Aust Prescr 2003;26:94-5) and crizotinib (Aust Prescr, published online 2014 Apr 16), afatinib is a tyrosine kinase inhibitor approved for advanced or metastatic non-small cell lung carcinoma. Afatinib irreversibly binds to the ErbB family of epidermal growth factor receptors – ErbB1 (epidermal growth factor receptor or EGFR), ErbB2 (human epidermal growth factor receptor 2 or HER2), ErbB3 and ErbB4. By blocking signalling from these molecules, afatinib slows down the growth and spread of tumour cells.

About 10% of Australian patients with non-small cell lung carcinoma have mutations in the EGFR gene. These are activating mutations which contribute to the malignant phenotype – the two most common are Del 19 (deletion in exon 19) and L858R (point mutation in exon 21). Afatinib is only approved for patients who have tumours with these mutations.

An open-label phase III comparative trial assessed the efficacy of afatinib (40 mg once a day) as a first-line treatment in 345 patients with an activating mutation in their EGFR gene. A subgroup of 308 patients had the Del 19 or L858R mutation. After a median of 11 months, afatinib significantly prolonged median progression-free survival compared to chemotherapy (see Table). In the afatinib group, progression-free survival was 2.5 months longer in those with Del 19 or L858R mutations. Afatinib did not significantly prolong overall survival compared to chemotherapy.[1]

In a questionnaire about symptoms, the onset of cough (p=0.007) and dyspnoea (p=0.015) was significantly delayed with afatinib compared to chemotherapy. However, diarrhoea, dysphagia and sore mouth were reported to be worse.[2]

A phase II trial in lung adenocarcinoma found that median progression-free survival was slightly longer for patients who received afatinib first-line compared to those who received afatinib after chemotherapy had failed (see Table).[3] In a subgroup of 23 patients who did not have the Del 19 or L858R mutation, median progression-free survival was only 3.7 months.[3]

In a trial of 62 patients who had become resistant to previous treatment with erlotinib, gefitinib or both, response to afatinib treatment was poor (5 partial responses). Mean treatment duration was 4.6 months and median progression-free survival was 4.4 months.[4]

Table **Efficacy of afatinib in advanced non-small cell lung carcinoma**

	Phase III trial[1]	
	afatinib	**chemotherapy** (cisplatin plus pemetrexed)
Number of patients	229	115
Progression-free survival:		
• all patients (n=345)	11.1 months	6.9 months
• patients with exon 19 deletion or L858R mutation (n=308)	13.6 months	6.9 months
Response rate (complete or partial)	56%	23%
Median overall survival		
• patients with exon 19 deletion or L858R mutation (n=308)	30.3 months	26.2 months
	Phase II trial[3]	
	first-line afatinib	**second-line afatinib**
Number of patients	61	68
Progression-free survival	12 months	8 months
Response rate (complete or partial)	66%	57%
Median overall survival	not reached	23.3 months

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary. At the time of publication, there may be limited published data and little experience in Australia of safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

Adverse reactions to afatinib were very common with approximately half of the participants having at least one serious adverse event (grade 3 or more). Rash (16.2% of people), diarrhoea (14.4%), paronychia (11.4%) and stomatitis/mucositis (8.7%) were the most common serious events.[1]

Almost everyone who takes afatinib develops diarrhoea so it is important to warn patients of this. Pre-emptive antidiarrhoeal drugs, such as loperamide, can be prescribed and should be started as soon as symptoms occur. Monitoring of serum electrolytes may be needed depending on the severity and duration of diarrhoea, and the afatinib dose may need to be reduced, interrupted or stopped. Dose changes should also be considered for severe skin reactions, such as bullous, blistering and exfoliative skin conditions.

Interstitial lung disease has been reported with afatinib and has been fatal in some cases. Sudden onset or worsening dyspnoea, cough or fever should be investigated and treatment stopped if it is diagnosed. Severe hepatic impairment has also been reported so regular monitoring of liver function is recommended.

Referral to an ophthalmologist should be considered for patients who develop eye symptoms such as inflammation, lacrimation, blurred vision, light sensitivity or pain, as ulcerative keratitis can occur. Contact lenses increase the risk of these adverse events.

Inhibitors of HER2 have been associated with left ventricular dysfunction so cardiac monitoring should be considered in patients who have risk factors.

Women of childbearing age should avoid becoming pregnant while taking afatinib as it has the potential to cause fetal harm. In animal studies, afatinib was excreted in breast milk so breastfeeding is not recommended.

Following oral administration, peak plasma concentrations of afatinib are reached within 2–5 hours. The terminal half-life is 37 hours with the dose being excreted in the faeces (85%) and urine (4%). Exposure to afatinib is increased in women, those with a low body weight and those with renal impairment so closer monitoring for adverse effects is recommended for these patients. Afatinib is not recommended if renal or hepatic impairment is severe.

Drug exposure is decreased when afatinib is taken with a high-fat meal so food should be avoided for at least three hours before and one hour after taking a dose. The recommended starting dose of 40 mg a day can be escalated to 50 mg a day. However, there is no extra proven benefit at this dose and adverse events are more common.[3]

Afatinib is a substrate for P-glycoprotein so strong inhibitors and inducers of this transporter may affect plasma concentrations. Strong inhibitors (such as ketoconazole, erythromycin and verapamil) should only be administered at the same time or after the afatinib dose.

Afatinib adds to the treatment options for patients with non-small cell lung cancer, but patients must have the Del 19 or L858R mutation to qualify for treatment. Afatinib slows disease progression when used first-line or after chemotherapy, but showed little benefit in patients who had previously been treated with erlotinib or gefitinib. As with other drugs in this class, severe, and sometimes fatal, adverse reactions to afatinib can occur and often limit treatment.

T manufacturer provided the product information

REFERENCES *†

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).