Erlotinib (NSCLC)

Indication

First line treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) for patients who test positive for the epidermal growth factor receptor tyrosine kinase (EGFRTK) mutation.
(NICE TAG 258).

As an alternative to docetaxel as a second-line treatment option for patients with non-small cell lung cancer (NICE TAG 162).

ICD-10 codes

Codes with a prefix C34

Regimen details

Day	Drug	Dose	Route
1-28	Erlotinib	150mg OD	PO

Cycle frequency

Continuously until disease progression or unacceptable toxicity.

Number of cycles

As above

Administration

Erlotinib is available as 25 mg, 100 mg and 150 mg film-coated tablets.
The dose should be taken once daily at least one hour before or two hours after food.
Tablets should not be crushed.

Grapefruit and grapefruit juice should be **avoided** whilst taking erlotinib.

Patients should be encouraged to use a regular moisturiser at the start of erlotinib treatment to prevent and minimise problems with skin dryness.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential (no routine antiemetics required)

Additional supportive medication

Loperamide should be prescribed to be used if required.
Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment to minimise the risk of dry skin.

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

Investigations – pre subsequent cycles

Clinical review is recommended after 2 weeks, and then at a minimum of 4 week intervals until stabilisation of toxicities. Once this is achieved this period may be extended.

Investigation	**Validity period** (or as per local practice)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils*	≥ 1.0 x 10^9/L
Platelets*	≥ 100 x 10^9/L
Creatinine clearance (CrCl)	Serum creatinine < 1.5 x ULN
AST/ALT	< 5 x ULN
Bilirubin	< 3 x ULN

* see haematological toxicity below

Dose modifications

Tumour flare can occur after stopping erlotinib. This needs to be considered during dose interruptions or discontinuation of erlotinib, particularly in the presence of CNS metastases or other situations where minor increase in tumour size can have a significant effect. Discuss with consultant.

- **Haematological toxicity**

Erlotinib is not myelosuppressive.
Patients may continue to take erlotinib during periods of myelosuppression.

- **Renal impairment**

There is no data available to support the use of erlotinib in patients with CrCl < 15 mL/min and so it should not be used in such patients.

- **Hepatic impairment**

Erlotinib is primarily cleared via the liver. It should be used with caution in hepatic impairment and is contraindicated in patients with severe hepatic impairment.

Dose interruptions and/or reductions may be required for hepatic toxicity. Fatal hepatic toxicity has been recorded with erlotinib.

- **Other toxicities**

Any patient with grade 3 or 4 toxicity not controlled by optimum supportive care will require a dose reduction as per the table below:

Level	Erlotinib dose
Starting dose	150mg OD
1st dose reduction	100mg OD
2nd dose reduction	50mg OD

Dose modification for skin rash

Typical erlotinib skin rash is described as:

- Pustular/papular appearance
- Usually involves face, head and upper torso
- May be secondarily infected as diagnosed by a tan/brown crust overlying inflammatory lesions with significant oozing of fluid and or an abrupt change to the appearance of lesions (particularly if they differ from those in other areas)

Toxicity grade	Definition	Dose adjustment/management
1-2	Generally localised Minimal symptoms No sign of infection	100% dose Treat with simple emollients
3	Generalised Moderate symptoms No sign of infection	Dose interruption may be required Treat as above. Consider oxytetracycline 500mg BD Review after 2 weeks.
4	Generalised Severe symptoms Potential for infection Significant impact on daily life	Dose interruption for 7-14 days. Restart with 50mg dose reduction. Discontinuation may be necessary. Treat as above. Consider oral prednisolone 25mg OD for 1 week then reducing by 5mg per day over 5 days. Review after 2 weeks.

Other supportive management may include antihistamine and pain relief.

Topical retinoids and other acne treatments are NOT recommended as the rash is not acne. They may exacerbate the rash (due to their skin drying effects).

Dose modification for diarrhoea

50% patients taking Erlotinib experience some diarrhoea.

Toxicity grade	Dose adjustment/management
1-2	100% dose Loperamide
3	If unresponsive to antidiarrheal medication for 24 hours, stop drug until <grade 1 and recommence with 50mg dose reduction. Loperamide
4	If unresponsive to antidiarrheal medication for >24 hours, discontinue. Loperamide

In more severe or persistent cases of diarrhoea leading to dehydration erlotinib treatment must be stopped and appropriate measures should be taken to intensively rehydrate the patients intravenously.

Around 1 in 100 patients taking erlotinib develop Interstitial Lung Disease like events (which can be fatal). Patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, should have their erlotinib interrupted pending diagnostic evaluation.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

GI bleeding
Stevens-Johnson syndrome/toxic epidermal necrosis
Interstitial lung disease

- **Frequently occurring side effects**

Diarrhoea
Rash
Anorexia
Fatigue
Elevated LFTs

- **Other side effects**

Nil

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin): avoid co-administration these may increase plasma concentrations of erlotinib.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of erlotinib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to erlotinib.

Coumarin anticoagulants, e.g. warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.

Drugs that reduce gastric acidity: reduce the solubility of erlotinib, thereby reducing its absorption. The manufacturers advise against the concurrent use of proton pump inhibitors or H2-receptor antagonists. If the use of ranitidine is essential, administration should be separated, with the erlotinib taken 2 hours before, or 10 hours after, the ranitidine. Although antacids are also predicted to interact, antacid interactions can usually be minimised by separation of administration. The manufacturer recommends that, if treatment with antacids is essential, they should be taken at least 4 hours before, or 2 hours after, erlotinib.

Additional comments

Smoking may reduce the effectiveness of erlotinib so patient should be advised to stop if possible.

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 258 accessed via www.nice.org.uk (04 June 2014)
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 162 accessed via www.nice.org.uk (04 June 2014)
- Summary of Product Characteristics – Erlotinib (Roche) accessed via www.medicines.org.uk (04 June 2014)
- Shepherd FA et al. Erlotinib in previously treated non-small cell lung cancer. NEJM 2005;353:123-132

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