ERLOTINIB (TARCEVA®) FOR NSCLC

Cumbria, Northumberland, Tyne & Wear Area Team

DRUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Cycle length</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 to 28</td>
<td>Continuous</td>
<td>Erlotinib</td>
<td>150 mg</td>
<td>Oral</td>
<td>ONCE daily</td>
</tr>
</tbody>
</table>

DOSE FORM
Presented as 25mg, 100mg and 150mg Tablets

CYCLE LENGTH AND NUMBER OF DAYS
One 150mg dose orally, taken ONCE daily until disease progression.

APPROVED INDICATION(S)
Patients with locally advanced or metastatic non-small cell lung cancer after failure of first line chemotherapy regimen as an alternative 2nd line treatment to Docetaxel (Taxotere)

Erlotinib is also approved from Cancer Drug Fund (CDF) as a 3rd line treatment after failure of Docetaxel (Taxotere). Note: this indication is not funded through normal NHS funding. Trusts must ensure 3rd line patients are identified, a CDF registration form completed and finance departments aware.

ELIGIBILITY CRITERIA
- Locally advanced / metastatic NSCLC after failure of 1 prior chemotherapy regime
- PS 0, 1, 2.
- Radiologically or clinically evaluable disease
- Able to take oral medication
- Using effective contraception if of reproductive potential

EXCLUSION CRITERIA
- Chemotherapy naïve patients
- Pregnant or lactating women
- Concurrent uncontrolled medical illness
- Impaired renal function (Serum creatinine>5 x ULN)
- Impaired hepatic function (Bilirubin > 2 x ULN, ALT>2 x ULN in absence of liver mets and > x 5ULN with liver mets)

PREMEDICATION
None

RECOMMENDED TAKE HOME MEDICATION
- Metoclopramide 10 three times daily as required (not usually needed)
- Loperamide 2mg prn (max 16mg in 24 hours) for diarrhoea as required
- Emollients (for skin rash) e.g. Diprobase, Epaderm, E45, Neutrogena * encourage patients to use regularly to prevent skin dryness.
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INVESTIGATIONS / MONITORING REQUIRED
Baseline chest X-ray/ CT scan, FBC, U&E, LFT’s & tumour markers as appropriate prior to starting treatment and at appropriate intervals during treatment.

ASSESSMENT OF RESPONSE
Radiological and clinical assessment will be performed at baseline and then 8 weeks following commencement of erlotinib. Erlotinib will only be continued if response is documented. Assessment will thereafter be at 3 to 4 monthly intervals

REVIEW BY CLINICIAN
Assessment of response at 8 weeks and then at 3 to 4 monthly intervals or sooner as appropriate to individual patient.

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local practice.

ADMINISTRATION NOTES
- Taken with water 1 hour prior to or 2 hours after food
- Avoid strong sunlight or use a good sunscreen SPF 15 or higher
- Hepatic cytochromes CYP3A4 and CYP1A2 are involved in the metabolism of erlotinib. Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 and CYP1A2 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided.
- Patients are advised to avoid grapefruit or grapefruit juice, because it inhibits CYP450 3A4, leading to increased plasma levels of erlotinib.
- Drugs that are CYP3A4 inhibitors include systemic anti-fungals e.g. ketoconazole, itraconazole, voriconazole; ciprofloxacin, protease inhibitors, erythromycin, clarithromycin and SSRI’s e.g. fluoxetine, fluvoxamine. If necessary the dose of erlotinib should be reduced, particularly if toxicity is observed.
- Drugs that are CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine, rifampin, phenobarbital or Hypericum perforatum (St Johns wort) may increase metabolism and decrease erlotinib plasma concentrations and hence potentially decrease efficacy.
- As bleeding events were observed in the BR21 study when patients were taking concurrent warfarin it has been suggested that there may be a possibility of an interaction, However no formal interaction studies with warfarin have been performed. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.
- Cigarette smoking increases erlotinib clearance, reducing erlotinib exposure by 50-60%. Efficacy and long term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes (and so is not recommended). Therefore, current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced.
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• Erlotinib solubility is altered by acidity of the upper GI tract, therefore drugs affecting pH, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for the loss of exposure. **Combination of erlotinib with proton pump inhibitors should be avoided as AUC was reduced by around 50%**. Administration of H2 antagonists at the same time as erlotinib also reduce absorption significantly. If an H2 antagonist (or proton pump inhibitor) is required they should be taken 10 hours before or 2 hours after erlotinib – this reduces the reduction in absorption for H2 antagonists to around 15%. The effects of concomitant administration of erlotinib with antacids are unknown; however, reduced bioavailability is likely. Administration of antacids and erlotinib should be avoided - if the combination is considered necessary the antacid should be taken at least 4 hours before or 2 hours after erlotinib.

• Erlotinib in combination with NSAIDs or steroids increases the risk of gastric perforation, and so should be avoided where possible.

• Around 1 in 100 patients taking erlotinib develops 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.

**TOXICITIES**

• Skin Reactions (see under dose modification below)
• Diarrhoea (see under dose modification below)
• Fatigue
• Nausea & vomiting (Note: if the patient vomits after taking an erlotinib tablet, the patient should NOT take another tablet, until the next dose is due.)
• Gastrointestinal perforation (rare)
• Interstitial Lung Disease

**DOSE MODIFICATION / TREATMENT DELAYS**

All dose modifications must be made by an oncology specialist following the recommended dose reduction strategy below.

<table>
<thead>
<tr>
<th>Level</th>
<th>Erlotinib (Tarceva) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>150mg daily</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; reduction</td>
<td>100mg daily</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; reduction</td>
<td>50mg daily</td>
</tr>
</tbody>
</table>

All toxic events will be graded according to NCI CTCAE v3.0 criteria plus the following scale for describing rash.

| Grade 1 | asymptomatic, macular or papular erythematous eruption in acneiform distribution; |
| Grade 2 | like grade 1 but with symptoms such as pruritus; |
| Grade 3 | extension of the eruption beyond the acneiform distribution of head, chest and back or the development of confluent lesions, painful lesions, or minor ulceration; |
| Grade 4 | exfoliative or ulcerating dermatitis. |

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In the event of any grade 3 or 4 toxicity that is not controlled by optimal supportive care (see below for guidelines) then dose reduce to the next dose level. Toxicity must improve by at least 1 NCI CTCAE grade within 2 weeks or further dose reduction by 1 level will be required. Once a patient has had a dose reduction the dose will not be re-escalated except after resolution of the skin rash.

DOSE ADJUSTMENT FOR SKIN RASH

Typical erlotinib rash has the following appearance:

- Pustular/ papular appearance and usually involves the face, head and upper torso.
- Erlotinib rash may be secondarily infected as diagnosed by:
  - A tan/brown crust overlying inflammatory lesions, with significant oozing of fluid
  - And/or an abrupt change in the appearance of lesions (particularly if they differ from those in other areas).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Symptoms</th>
<th>Dose modification</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2</td>
<td>Generally localised Minimally Symptomatic No sign of infection</td>
<td>none</td>
<td>Topical hydrocortisone 1% and/or topical clindamycin 1% lotion/gel (non-alcoholic basis),</td>
</tr>
<tr>
<td>3</td>
<td>Generalised moderate symptoms No sign of infection</td>
<td>Interrupt treatment for 7 to 14 days</td>
<td>Topical hydrocortisone 1% or short course of oral prednisolone and/or topical clindamycin 1% lotion/gel (non-alcoholic basis) plus oral tetracycline antibiotic (see below)</td>
</tr>
<tr>
<td>4</td>
<td>Generalised Severe symptoms, potential for infection Significant impact on daily life.</td>
<td>Dose interruption for 7 to 14 days as for Grade 3 or discontinue</td>
<td>Topical eumovate (clobetasol butyrate 0.05%) or short course of oral Prednisolone (see below) and/or topical clindamycin 1% lotion/gel (non- alcoholic basis) plus an oral tetracycline antibiotic (see below)</td>
</tr>
</tbody>
</table>

Choice of tetracycline

Oxytetracycline (500 mg twice daily) or lymecycline (408 mg once daily), a long acting tetracycline are the preferred oral tetracyclines. Doxycycline 100mg daily has potential for photosensitivity so should be avoided in patients with high UV exposure. Minocycline 100 mg BD can also be used, but can cause adverse drug reactions including pigmentation.

Steroid regimen

Start with prednisolone 25 mg for 1 week; reduce by 5 mg/day over 4 days. Assess patient response and need for ongoing steroid treatment.

Other supportive medicines

- Consider adding in antihistamines e.g. chlorphenamine/ hydroxyzine and painkillers, paracetamol/ ibuprofen if itching and or painful.
- Topical retinoids and other acne medications (eg benzyl peroxide) are NOT recommended since rash is not acne. Their skin drying effects may exacerbate rash.
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DOSE ADJUSTMENT FOR DIARRHOEA
Diarrhoea has occurred in 50% of patients on erlotinib.

<table>
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<tr>
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<th>Dose modification</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2</td>
<td>none</td>
<td>Loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day)</td>
</tr>
<tr>
<td>3</td>
<td>If unresponsive to antidiarrhoeal medication for 24 hours then stop drug until resolution to grade &lt;1 and then restart at next dose level down</td>
<td>Loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day)</td>
</tr>
<tr>
<td>4</td>
<td>If unresponsive to antidiarrhoeal agent for &gt;24 hours then discontinue drug</td>
<td>Loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day)</td>
</tr>
</tbody>
</table>

Note: 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.

TREATMENT LOCATION
Cancer Centre and Cancer Units

REFERENCES:

Document Control

<table>
<thead>
<tr>
<th>Document Title:</th>
<th>NECN Regimen erlotinib (Tarceva) for NSCLC v3</th>
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<tbody>
<tr>
<td>Document No:</td>
<td>CRP-07-L018</td>
</tr>
<tr>
<td>Current Version:</td>
<td>3.1</td>
</tr>
<tr>
<td>Author:</td>
<td>Steve Williamson Consultant Pharmacist</td>
</tr>
<tr>
<td>Approval Signature*:</td>
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<tr>
<td>Approved by:</td>
<td>Dr Jill Gardner Consultant Medical Oncologist NCC</td>
</tr>
<tr>
<td>Date Approved:</td>
<td>29.05.14</td>
</tr>
<tr>
<td>Due for Review:</td>
<td>May 2016</td>
</tr>
<tr>
<td>Summary of Changes:</td>
<td>1.2 Changed format titles to reflect new style; Added extra detail</td>
</tr>
<tr>
<td></td>
<td>1.3 Changed topical steroid recommendations</td>
</tr>
<tr>
<td></td>
<td>2.0a Document number updated. A number of drug interactions and additional administration notes added.</td>
</tr>
<tr>
<td></td>
<td>3.0 Document number updated to reflect latest guidance on cutaneous toxicity (reference 6) and CDF approval for 3rd line.</td>
</tr>
<tr>
<td></td>
<td>3.1 Protocol reviewed and reissued.</td>
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