Lapatinib (Tyverb®) plus Capecitabine (Xeloda®)
Cumbria, Northumberland, Tyne & Wear Area Team

DRUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 to 21</td>
<td>Lapatinib</td>
<td>1250mg <em>ONCE a day</em></td>
<td>Oral</td>
<td>N/A</td>
<td>Continuous</td>
</tr>
<tr>
<td>Days 1 to 14</td>
<td>Capecitabine</td>
<td>1000 mg/m² <em>twice a day</em></td>
<td>Oral</td>
<td>N/A</td>
<td>14 days on, 7 days off</td>
</tr>
</tbody>
</table>

*Please note:* The dosage schedule when lapatinib is used as a single agent (i.e. in combination with an aromatase inhibitor) is different.

DOSE FORM

Capecitabine is supplied as 150mg and 500mg tablets, therefore calculated doses must be rounded to the nearest 150mg.

Lapatinib is supplied as 250 mg film-coated tablets.

CYCLE LENGTH AND NUMBER OF DAYS

- 21 days, until disease progression
- Oral capecitabine given from day 1 to 14, twice daily, then 1 week off

APPROVED INDICATION

In combination with capecitabine for patients with advanced or metastatic breast cancer patients whose tumours overexpress HER2 (ErbB2) and who have disease progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

ELIGIABILITY CRITERIA

Breast cancer patients with adequate renal and cardiac function.

EXCLUSION CRITERIA

- Patients incapable of managing oral chemotherapy themselves or with the assistance of a carer
- Patients with swallowing difficulties
- Significant cardiac risk factors for development of CHF

RECOMMENDED TAKE HOME MEDICATION

Metoclopramide 10 mg three times daily as required

INVESTIGATIONS / MONITORING REQUIRED

Pre treatment: Assessment of renal and hepatic function, FBC, and cardiac history. **Note** as patients will have been previously treated with trastuzumab (herceptin) they must continue with ongoing cardiac monitoring e.g. 3 or 4 monthly echocardiogram. .

Prior to each cycle  FBC, U&E, LFT's & tumour markers as appropriate
Where CEA is elevated this should be measured before each cycle.

ASSESSMENT OF RESPONSE

Metastatic: Tumour size and patient symptomatic response
REVIEW BY CLINICIAN
To be reviewed by a nurse, a pharmacist or a clinician before every cycle.

NURSE / PHARMACIST LED REVIEW
On cycles where not seen by clinician.

ADMINISTRATION NOTES

- Decreases in left ventricular ejection fraction have been reported. The majority of decreases are observed within the first 9 weeks, but may also occur over 6 months after lapatinib initiation. It appears that cardiac effects of lapatinib may be similar to trastuzumab, which are generally reversible and non-progressive.
- Advise patients of the risk of hand-and-foot skin-reaction (palmar/plantar erythrodysesthesia) and that they should stop taking treatment and contact their chemotherapy unit if they have pain, swelling, and redness of hands and/or feet.
- Diarrhoea is common, and may require intervention with fluids and electrolytes if severe. If diarrhoea is a problem give loperamide 2 to 4 mg four times daily as required or codeine phosphate 30mg four times daily (see below)
- Since Lapatinib is extensively metabolized by CYP3A4, avoid concomitant use of strong CYP3A4 inhibitors and inducers:
  - Concomitant administration with potent inhibitors of CYP3A4 activity (e.g. ketoconazole, voriconazole, protease inhibitors, clarithromycin) may increase lapatinib plasma concentrations.
  - Drugs that are CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine, rifampin, phenobarbital or Hypericum perforatum (St John’s Wort) may increase metabolism and decrease lapatinib plasma concentrations and hence potentially decrease efficacy
- Avoid grapefruit and grapefruit juice while on lapatinib treatment
- The solubility of lapatinib is pH-dependent. Concomitant treatment with substances that increase gastric pH should be avoided, antacids, proton pump inhibitors etc as lapatinib solubility and absorption may decrease.
COUNSELLING POINTS FOR ORAL LAPATINIB AND CAPECITABINE

How to take:
- **Capecitabine**: Take tablets 12 hours apart, within 30 minutes after the end of meal (i.e. breakfast & evening meal.) Swallow whole with water
- **Lapatinib**: Taken either at least one hour before, or at least one hour after food.

Side effects
Common side effects to discuss with patient include: diarrhoea, nausea & vomiting, rash, hand-foot syndrome (painful red swelling in hands and feet), fatigue, fever or infection. If patients notice any of these advise them to stop taking treatment, contact doctor/chemotherapy day unit who will take steps to manage side effects and advise on continuing treatment.

COUNSELLING POINTS FOR ORAL LAPATINIB AND CAPECITABINE (continued)

Missed dose:
If remember half an hour after they should have taken their tablets, then take the missed dose, otherwise only take the regular dose at next scheduled time. Do not double-up doses to make up for the missed doses or take extra doses at the end of the treatment cycle.

Post dose vomiting:
In the case of vomiting within a few hours after drug intake, never repeat the administration of the dose.

Storage/ Disposal
Both tablets should be stored in cool dry place less than 30°C. Unused medicines must be returned to hospital pharmacy for disposal

TOXICITIES

- Rash
- Nausea and Vomiting
- Diarrhoea
- Palmar/Plantar Erythrodynesthesi - Can be severe, patients must be forewarned
- Bone Marrow Suppression
- Fatigue
- Stomatitis
- Cardiotoxicity
- Rarely Interstitial lung disease / pneumonitis
- Hepatotoxicity

DOSE MODIFICATION / TREATMENT DELAYS

Haematological Toxicity:
- ANC < 1.0 to 1.5 and/or platelets <100, delay for 1 week
- >1 week recovery, dose reduce capecitabine by 25%
- If further delays necessary consider further dose reduction (discuss with SpR/Consultant) or consider stopping treatment

Non-Haematological Toxicity

Lapatinib Dosage Adjustment for Toxicity:
Suggested dose levels for lapatinib are 1250 mg, 1000 mg, 750mg and 500mg.
Dose adjustment according to cardiac function for lapatinib

<table>
<thead>
<tr>
<th>LVEF</th>
<th>Absolute decrease of &lt;10%</th>
<th>Absolute decrease of 10-15%</th>
<th>Absolute decrease of ≥16%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Continue</td>
<td>Continue</td>
<td>Hold*</td>
</tr>
<tr>
<td>1-5% below normal limits</td>
<td>Continue</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>≥ 6% below normal limits</td>
<td>Continue</td>
<td>Hold</td>
<td>Hold</td>
</tr>
</tbody>
</table>

Note these are the same monitoring criteria as for trastuzumab, seek expert advice for management of patients with altered LVEF

Table of Lapatinib and capecitabine dose adjustments according to CTC toxicity (non-haematological and not PPE/hand/foot)

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose with prophylaxis and reduce Lapatinib by 1 dose level.</td>
</tr>
<tr>
<td></td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose and reduce Lapatinib by a further dose level.</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; appearance</td>
<td>Discontinue treatment</td>
<td></td>
</tr>
</tbody>
</table>

Table of Diarrhoea toxicity grading for capecitabine only

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Toxicity</th>
<th>% 5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diarrhoea (watery stool 2-3 times/day)</td>
<td>Hold until recovery, then resume at 100% dose for remainder of course</td>
</tr>
<tr>
<td>2</td>
<td>Diarrhoea (watery stool 4-6 times/day)</td>
<td>Hold until recovery, then resume at 75% capecitabine dose and 100% Lapatinib. Note dose reduce Lapatinib on second or subsequent grade 2 toxicity.</td>
</tr>
<tr>
<td>3/4</td>
<td>Diarrhoea (watery stool &gt;7 times/day)</td>
<td>Following grade 3 or 4 diarrhoea, subsequent doses of both drugs should be decreased or treatment discontinued permanently (grade 4).</td>
</tr>
</tbody>
</table>

*see manufacturer’s datasheets for full details
Capecitabine is renally excreted; therefore dose requires adjustment for patients with moderate renal impairment (<50ml-30ml/min) require a 25% dose reduction. Contra-indicated in severe renal failure (CrCl <30ml/min) (Cockcroft & Gault)

**Hepatic Function**
Discontinue lapatinib permanently in patients who develop severe changes in liver function. Administration of lapatinib to patients with moderate to severe hepatic impairment should be undertaken with caution due to increased exposure to the medicinal product.

**SKIN Toxicity (Non-Handfoot/PPE)**
The Rash that occurs with lapatinib can seen as a class effect of EGFR inhibitors. Typical EGFR-TK Inhibitor rash has the following appearance:

- Pustular/papular appearance and usually involves the face, head and upper torso.
- Lapatinib 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>
</table>
| 1 to 2   | Generally localised
Minimally Symptomatic
No sign of infection | none | Topical hydrocortisone 1% and/or topical clindamycin 1% lotion/gel (non-alcoholic basis), |
| 3        | Generalised moderate symptoms
No sign of infection | Interrupt treatment for 7 to 14 days | 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) |
| 4        | Generalised Severe symptoms, potential for infection Significant impact on daily life. | Dose interruption for 7 to 14 days as for Grade 3 or discontinue | Topical Eumovate (clobetasol butyrate 0.05%) or short course of oral Prednisolone and/or topical clindamycin 1% lotion/gel (non-alcoholic basis) plus an oral tetracycline antibiotic (see below) |

**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.
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.

**TREATMENT LOCATION**

Can be given at Cancer Centre or Cancer Unit

**REFERENCES:**

- Lapatinib (Tykerb®) Product Monograph: GSK: Available at Medicines.org.uk