LAPATINIB + CAPECITABINE

For use in patients with advanced or metastatic HER2+ve breast cancer who have progressed on prior therapy

There is no NHS funding for the lapatinib and this needs to be supplied on a private prescription
(see St Luke's Cancer Alliance Operational Policy for Parallel Provision of NHS and Privately Funded Chemotherapy)

Drug/Dosage:	Lapatinib	1250mg (fixed dose)	PO once daily continuous
	Capecitabine	1000mg/m^2	PO twice daily from Day 1 to Day 14, followed by 7 days rest (i.e. 21 day cycle)

Administration: Lapatinib is available as 250mg tablets, which should be taken either at least one hour before, or at least one hour after food, at the same time of day each day.
Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal.
Grapefruit and grapefruit juice should be avoided while taking lapatinib.

Frequency: 3 weekly cycle until progression or unacceptable toxicity
CT scan after 3 months

Main Toxicities: myelosuppression; diarrhoea (due to both lapatinib and capecitabine); palmar-plantar erythema (PPE); rash; stomatitis; cardiotoxicity (uncommon); pulmonary toxicity due to lapatinib (rare); ovarian failure/infertility

Anti- emetics: mildly emetogenic

Regular Investigations:	FBC	Day 1
	U&Es*	Day 1 (*renal function should be closely monitored)
	LFTs	Day 1
	CA 15-3	On alternate cycles **only** if elevated prior to treatment.
	ECG	If previous history of angina, MI or rhythm disturbances
	Echo*/MUGA scan	baseline; at 4 and 8 months, then every 6 months thereafter Patients who develop asymptomatic cardiac dysfunction will require more frequent monitoring e.g. every 6–8 weeks.

* An echocardiogram is the preferred test, but whichever test is used initially for an individual, should ideally be used throughout

Comments: Ensure patients have a supply of loperamide, as diarrhoea is very common.

Lapatinib Interactions: Concomitant use of CYP3A4 enzyme inducers (e.g. phenytoin, rifampicin, carbamazepine, St John's Wort) with lapatinib should be avoided, as this may increase the risk of therapeutic failure.

Co-administration of lapatinib with strong CYP3A4 inhibitors (e.g. itraconazole, posaconazole, clarithromycin) should be avoided. If this is not possible, the dose of lapatinib may need to be reduced according to tolerability.
Co-administration of lapatinib with moderate CYP3A4 inhibitors (e.g. erythromycin, fluconazole, diltiazem, verapamil) should proceed with caution and adverse reactions carefully monitored.

Reason for Update: updated for use in patients who "top up" their lapatinib; frequency of monitoring LVEF in line with trastuzumab for advanced disease	Approved by Consultant: Dr T Crook
Version: 2	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 1	Date: 14.9.17
Prepared by: S Taylor	Checked by: C Tucker

Grapefruit and grapefruit juice should also be avoided while on lapatinib, as this may increase lapatinib toxicity.

The solubility of lapatinib is pH-dependent. Concomitant treatment with substances that increase gastric pH (e.g. PPIs or ranitidine) should be avoided, as lapatinib solubility and absorption may decrease.

Lapatinib has been shown to increase digoxin levels (80% increase in AUC), so consider a dose reduction of digoxin and monitor digoxin levels closely when initiating lapatinib.

Dose Modifications

Haematological Toxicity:	Neutrophils < 1.5 x 10^9/l or Platelets < 100 x 10^9/l	Delay capecitabine for 1 week, but continue lapatinib. Repeat FBC. If recovered, restart capecitabine, using dose adjustment guidelines in table below, according to worst grade of haematological toxicity recorded.

Non-Haematological Toxicities:

Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.

Toxicity due to capecitabine may be managed symptomatically and/or modification of the dose (treatment interruption or dose reduction). Use the table below for dose adjustment guidelines. Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

Haematological and Non-Haematological Dose Adjustment Guidelines for Capecitabine according to Common Toxicity Criteria

Common Toxicity Criteria	During Course of Therapy	Dose adjustment for next cycle (% of start dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2: 1st Appearance	Interrupt until resolved to Grade 0 – 1	Give 100% dose
Grade 2: 2nd Appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 2: 3rd Appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 2: 4th Appearance	Discontinue treatment permanently	
Grade 3: 1st appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 3: 2nd appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 3: 3rd appearance	Discontinue treatment permanently	
Grade 4: 1st appearance	Discontinue permanently **or, with Consultant approval,** interrupt until resolved to Grade 0 – 1	Give 50% dose

Lapatinib-Induced Toxicities, including Rash and Diarrhoea	≥ Grade 2 toxicity	Interrupt lapatinib treatment. If first episode, re-start lapatinib at 1250mg/day, once toxicity resolved to Grade 1 or less. If recurring toxicity, re-start lapatinib at 1000mg/day. If in doubt, discuss with Consultant.

Renal Impairment: Before every cycle, creatinine clearance should be calculated using Cockcroft and Gault. If borderline, an EDTA should be requested.

CrCl (ml/min)	Capecitabine Dose
> 50	Give 100% dose
30 – 50	Give 75% dose
< 30	Omit

No dose adjustment for lapatinib is required in mild or moderate renal impairment (lapatinib undergoes extensive metabolism). However, there is no data in patients with severe renal impairment.

Hepatic Impairment:

Bilirubin > 3 x ULN or ALT/AST > 2.5 ULN	Omit capecitabine until liver function recovers

Use lapatinib with caution in patients with moderate to severe hepatic impairment. There are no specific dose adjustment recommendations, but the patient will be at increased risk of adverse events due to reduced clearance of lapatinib.

Cardiotoxicity: Cardiotoxicity has been associated with fluoropyrimidine therapy (including myocardial infarction, angina, arrhythmias, cardiogenic shock, sudden death and ECG changes). Therefore, exercise caution in patients with prior history of coronary heart disease, arrhythmias and angina pectoris.

Cardiac failure is associated with lapatinib, and caution should be exercised in treating patients who present with symptomatic heart failure, history of hypertension or documented coronary artery disease.

If patient shows a continued decrease in left ventricular function during treatment with lapatinib, but remains asymptomatic, consideration should be made to discontinuing therapy if no clinical benefit of lapatinib has been seen.

If symptomatic cardiac failure develops during lapatinib therapy, it should be treated with standard medications for this purpose. Lapatinib therapy should be discontinued until the LVEF recovers to normal and the patient is asymptomatic. Lapatinib may then be re-introduced with close monitoring at the reduced dose of 1000mg/day.

References:

Geyer, C et al; New Engl J Med 2006; 355: 2733-2743
Cameron, D et al; Breast Cancer Res Treat 2008; 112: 533-543

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