LONDON CANCER ALLIANCE
West and South

Breast Pathway Group – Lapatinib & Capecitabine in Advanced Breast Cancer

Indication:

Lapatinib in combination with capecitabine is recommended as a treatment option for advanced or metastatic breast cancer

National Cancer Drug Fund criteria:

- HER2 over-expressed (defined by IHC3+ or IHC2+ with gene amplification or gene amplification alone)
- Previous treatment with anthracyclines or anthracycline contra-indicated
- Previous treatment with taxanes
- Previous treatment with trastuzumab in the metastatic setting
- Use in combination with capecitabine

National Cancer Drug Fund application and approval is required prior to starting treatment

Regimen details:

Lapatinib	1250mg	PO	Continuous
Capecitabine	1000mg/m^2 BD	PO	Days 1 to 14 followed by 7 day rest period

Administration:

Lapatinib is available as a 250mg film coated tablet.
The daily dose of lapatinib should not be divided and should be taken either at least one hour before, or at least one hour after food. To minimise variability in the individual patient, administration of lapatinib should be standardised in relation to food intake, for example always to be taken one hour before a meal.

Capecitabine tablets orally twice a day, swallow whole with water within 30 minutes after a meal and approximately 12 hours apart.
Capecitabine is available as 500mg and 150mg tablets.

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Wendy Ng	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Lisa Yuen	Date prepared: November 2014 Review Date: November 2016

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.
©LCA Copyright 2014

Frequency:	Lapatinib is continuous Capecitabine taken from Days 1 to 14 every 21 days, continued until disease progression or unacceptable toxicity
Pre-medication:	Not applicable
Anti- emetics:	Low emetogenicity Follow local anti-emetic policy
Supportive medication:	Diarrhoea can be managed with loperamide Mouthcare as per local policy Topical emollients / suncare
Extravasation:	Not applicable

Regular investigations:

Prior to Cycle 1:

FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
MUGA/ECHO/ECG	See Comments

Prior to Day 1 (all cycles):

FBC	Day 1 (within 72 hours)
LFTs	Day 1 (within 72 hours)
U&Es	Day 1 (within 72 hours)

Toxicities: Diarrhoea, nausea, vomiting, dyspepsia, stomatitis, constipation, abdominal pain, anorexia, rash, hand-foot syndrome (palmar-plantar erythrodysesthesia), dry skin, pain in extremity and back, fatigue, mucosal inflammation, insomnia, headache, decreased LVEF, interstitial lung disease /pneumonitis, hyperbilirubinaemia and hepatoxicity

Cardiotoxicity: Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Wendy Ng	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Lisa Yuen	Date prepared: November 2014 Review Date: November 2016

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.
©LCA Copyright 2014

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Dose
≥ 1.5	&	≥ 100	100% dose
<1.5	or	<100	Delay for 1 week Repeat FBC - If recovered to above these levels, resume treatment at 100% doses. Dose reduction should be considered if myelosuppression results in delay of subsequent cycles

Non-haematological Toxicities

Renal Impairment

Creatinine Clearance (ml/min)	Capecitabine Dose	Lapatinib Dose
> 50	100%	100% No dose adjustment is necessary in patients with mild to moderate renal impairment.
30-50	Give 75%	
<30	Contra-indicated / omit	Caution is advised in patients with severe renal impairment (<30ml/min)

Hepatic Impairment

Capecitabine Dose	Lapatinib Dose
Clinical Decision In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis	Clinical Decision Use with caution in patients with moderate to severe hepatic impairment due to risk of increased exposure to the medicinal product. Discontinue if changes in liver function are severe; patients should not be retreated

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Wendy Ng	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Lisa Yuen	Date prepared: November 2014 Review Date: November 2016

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.
©LCA Copyright 2014

Non-haematological toxicities:

Lapatinib

Toxicity	Action	Dose Modification Recommendation Lapatinib
Pneumonititis/ interstitial lung disease	Hold and investigate	Discontinue if > Grade 3 confirmed as per CTC
Ejection Fraction <40% or LVEF lower than institution's lower limit of normal	Discontinue and monitor patient closely OR Resume after 2 weeks if LVEF ≥ normal and patient asymptomatic	Decrease Lapatinib to 1000mg once daily monitor closely. If recurs, discontinue.
Grade 2 Diarrhoea (Increase of 4-6 bowel movement/day over baseline)	Start loperamide, hold if required until resolved	No dose change required for lapatinib for the first 2 appearances, decrease to 1000mg once daily if recurs.
Grade 3 Diarrhoea (Increase of >7 bowel movement/day over baseline)	Hold until symptoms resolve, treat with loperamide	Re-start Lapatinib at 1000mg once daily when symptoms resolve
Grade 2 Rash	Continue Treatment	If not improved after 2 weeks, interrupt lapatinib treatment for up to 14 days. Re-start at full dose if symptoms resolves
Grade 3 Rash	Interrupt Treatment	If symptoms resolve within 14 days re start lapatinib at 1250mg daily If symptoms recur, interrupt treatment until resolve and restart lapatinib at 1000mg daily

Capecitabine

Dose modifications for diarrhoea, nausea, vomiting, stomatitis, and hand-foot syndrome (palmar-plantar erythrodysesthesia):

CTC Grade	1st Appearance Dose	2nd Appearance Dose	3rd Appearance Dose	4th Appearance Dose
0-1	100%	100%	100%	100%
2	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	delay* then 75%	delay* then 50%	discontinue	discontinue

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Wendy Ng	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Lisa Yuen	Date prepared: November 2014 Review Date: November 2016

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.
©LCA Copyright 2014

4	discontinue or delay* then 50%	discontinue	discontinue	discontinue

*stop treatment immediately and delay until toxicity resolved to grade 0-1

Cardiotoxicity:

Capecitabine:
Chest pain typical of myocardial ischaemia requires cessation of capecitabine and should be investigated.

Lapatinib:
Lapatinib has been associated with reports of decreases in left ventricular ejection fraction (LVEF) and has not been evaluated in patients with symptomatic cardiac failure. Caution should be taken if lapatinib is to be administered to patients with conditions that could impair left ventricular function (including co administration with potentially cardiotoxic agents).
Discontinue lapatinib in patients with symptoms associated with decreased left ventricular ejection fraction (LVEF) grade 3 or greater or if their LVEF drops below the institutions lower limit of normal.
Lapatinib may be restarted at a reduced dose of 1000mg/day when administered with capecitabine after a minimum of 2 weeks and if the LVEF recovers to normal and the patient is asymptomatic.

Prolongation of QT interval with lapatinib:
Caution should be taken if lapatinib is administered to patients with conditions that could result in prolongation of QTc (including hypokalaemia, hypomagnesemia, congenital long QT syndrome, or co administration of other medicines known to cause QT prolongation). Hypokalaemia or hypomagnesemia should be corrected prior to treatment. Electrocardiograms with QT measurement should be considered prior to administration of lapatinib and throughout treatment.

Interstitial lung disease/pneumonitis;

Lapatinib has been seen to cause interstitial lung disease/pneumonitis. Monitor for symptoms of pulmonary toxicity (dyspnoea, cough, fever) and treatment discontinued in patients who experience symptoms which are NCI CTCAE grade 3 or greater. Fatal cases have been reported.

Location of regimen

To be supplied to the patient for oral self-administration.

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.
©LCA Copyright 2014

delivery: Suitable for home delivery

Comments: Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced metabolism of capecitabine. Ensure patient is informed of action to take if signs of toxicity (e.g. severe mucositis, diarrhoea) develop within the first few days of treatment, as this is often an early indication of DPD deficiency.

Capecitabine contains anhydrous lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drug interactions: Significant interactions below. For full details consult product literature/reference texts.

Capecitabine:

- Allopurinol: avoid concomitant use (reduced efficacy of capectiabine)
- Warfarin/coumarin anticoagulants: switch to low molecular weight heparin (altered coagulation parameters and/or bleeding, including death)
- Phenytoin: monitor plasma phenytoin levels (increase phenytoin level)

Lapatinib:

- Co administration of lapatinib with strong inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone) should be avoided. Co administration of lapatinib with moderate inhibitors of CYP3A4 should proceed with caution and clinical adverse reactions should be carefully monitored.
- Co administration of lapatinib with known inducers of CYP3A4 (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort) should be avoided.
- Lapatinib is a substrate for the transport proteins Pgp and BCRP. Inhibitors (ketoconazole, itraconazole, quinidine, verapamil, ciclosporin, erythromycin) and inducers (rifampicin, St John's Wort) of these proteins may alter the exposure and/or distribution of lapatinib
- Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease.

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.
©LCA Copyright 2014

- Digoxin: Co-administration of lapatinib resulted in an approximate 80% increase in the AUC of digoxin.
- Food & drink: The bioavailability of lapatinib is increased up to about 4 times by food, depending on e.g. the fat content in the meal.
  Grapefruit juice may inhibit CYP3A4 in the gut wall and increase the bioavailability of lapatinib and should therefore be avoided during treatment with lapatinib

References:

GSK Ltd. Summary of Product Characteristics for Tyverb
Roche, Summary of product characteristics for Xeloda
A guide for Healthcare professionals to assist with the management of patients receiving TYBERB
Micromedex review: Lapatinib
Geyer C. E. et al (2006); NEJM, 255(26):2733-2743
SELCN Lapatinib Capecitabine protocol
NWLH Lapatinib Capecitabine protocol
NWLCN Breast Regimen Version 7 01
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009
LCA Breast Cancer Clinical Guidelines October 2013

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Wendy Ng	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Lisa Yuen	Date prepared: November 2014 Review Date: November 2016

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.
©LCA Copyright 2014