

Advancing nursing management approaches with new targeted therapies for ErbB2-positive metastatic breast cancer



Prior to the ECCO 15 – ESMO 34 Conference, an educational workshop for cancer nurses was held on Sunday 20th September 2009 in Berlin, Germany. The meeting was accredited by EONS with sponsorship provided by GSK. The purpose of the workshop was to discuss current knowledge behind clinical therapies in ErbB2-positive breast cancer, common side effects associated with these interventions and step-by-step proactive nursing management. Fifty four nurses from 12 countries across Europe attended the event and took part in interactive sessions with the various speakers.

Epidemiology and pathology of breast cancer

Annie Young, Nurse Director, 3-Counties Cancer Network (Gloucestershire, Herefordshire and South Worcestershire, UK). Past-president UK Oncology Nursing Society.

Despite many recent advances in diagnostic investigation technology and improvements in treatment and supportive care, breast cancer remains the leading cause of cancer-related mortality in European women¹. Evidence-based public health measures exist in many European countries to reduce mortality from breast cancer. National screening programmes that detect early invasive cancers have greatly improved early detection and hence survival rates¹. In Europe; Belgium, France and Sweden recorded the highest incidence (probably due to the presence of screening programmes), while the lowest incidence is to be found in countries, such as Cyprus, Belarus and the Ukraine¹.

Recent research has suggested patterns of gene expression may better predict prognosis and response to different types of cancer treatment². This research implies that there are four basic subtypes of breast cancer. The gene expression patterns of these cancers are comparable to the normal cells that line the lumen of breast ducts and glands². Luminal A and B cancer subtypes are both oestrogen receptor positive and are the most common². Luminal A cancers are associated with the best prognosis. Luminal B cells have a higher expression of proliferative genes such as ErbB2. They therefore grow more rapidly and are associated with a poorer prognosis³.

Amplification and over-expression of ErbB2 has been found to be associated with a median survival of 3 years³. ErbB2- (or HER2)-positive, oestrogen receptor negative breast cancers are less common but are also linked to a poor prognosis³. Basal type cancers are principally triple negative phenotype – that is to say they lack oestrogen and progesterone receptors and have low expression of ErbB2. The gene expression of these cells is akin to cells in the deeper basal layers of the breast ducts and glands. Basal type cancers tend to be high grade tumours that grow quickly and have a poor prognosis².

Growth factors and receptors

Growth factors (or ligands) may be characterised as protein “signals” circulating in the blood or near to the cells that secrete them and are typically present in low concentrations. They initiate various cellular activities by first binding with their associated receptor on the cell’s surface. There are about 58 tyrosine kinases which act as growth factor receptors⁴. When bound to the growth factor, the receptor triggers various processes within the cell such as cell division, development of blood vessels, blood vessel formation and embryonic development. The process of message transfer to initiate these intracellular activities is known as signal transduction – a complex and tightly regulated network of signal pathways, with many starting points and alternative routes for message transfer. The ErbB family of receptors are major regulators of cellular processes such as cell division, growth, differentiation, migration and survival. The family comprises four related transmembrane receptor tyrosine kinases (RTK’s) that bind to members of the epidermal growth factor

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(EGF) family to trigger these processes⁵. Malignant tumours, including breast cancer, may be a consequence of unregulated or dysregulated control of the ErbB signaling pathway by other genes⁵.

Approximately 20-30% of invasive breast carcinomas have ErbB2 over-expression or gene amplification³. This over-expression is associated with aggressive disease, poorer response to conventional cytotoxic chemotherapy and hormonal therapy resulting in a reduced survival time.

Strategies to inhibit ErbB2

A number of strategies have been developed to target the ErbB2 signalling pathway. However so far only monoclonal antibodies (mAbs) and small-molecule tyrosine kinase inhibitors (TKIs) have been developed to the greatest extent in a clinical setting. Trastuzumab (Herceptin[®]) is the only mAb currently licensed for use in ErbB2-positive breast cancer. Other mAbs under investigation for this indication include pertuzumab (Omnitarg[®]),

bevacizumab (Avastin[®]) and T-DM1. Trastuzumab binds to the extra cellular domain of the ErbB2 receptor, thereby preventing activation of the receptor. mAbs have limits to their activity in that they are specific to only one receptor (e.g. ErbB2)⁶ and they can only act outside the cell. Therefore, if a receptor does not have an extracellular domain, a monoclonal antibody might not be effective.

TKIs are small enough to enter the cell and block the activation of downstream signaling pathways. The TKI lapatinib (Tyverb[®]) is the only TKI currently licensed for use in ErbB2-positive breast cancer. Lapatinib binds with the intracellular tyrosine kinase domain of the ErbB2 receptor to block its activation and prevent signal transduction inside the cell. The same tyrosine kinase domain may be present on more than one type of receptor (e.g. ErbB1 and ErbB2). Therefore TKIs have the potential to be active against multiple receptors⁷. That TKIs can enter the cell and be active is significant in instances where no extracellular domain is present.⁸

Targeted therapies for ErbB2-positive breast cancer

Thomas Bogenrieder, GSK Clinical Director Oncology, Oncology Center of Excellence, Europe, Asia-Pacific, Japan & Emerging Markets

Trastuzumab (Herceptin[®]) was the first humanised monoclonal antibody to be developed to treat breast cancer. Compelling clinical trial evidence in metastatic and adjuvant settings has resulted in trastuzumab becoming a crucial component of therapy for ErbB2-positive breast cancer as both monotherapy and in combination with other cytotoxic agents.

Lapatinib (Tyverb[®]), an oral tyrosine kinase inhibitor (TKI), acts inside the cell to block growth and survival of breast cancer cells and may therefore also be active in cells which do not have an extracellular ErbB2 domain.⁸ Pre-clinical investigation of lapatinib has shown that it is a potent inhibitor of both the EGFR and ErbB2 receptors⁷. Dual receptor inhibition is a hopeful therapeutic strategy as it may potentially block multiple signalling pathways⁷. Lapatinib, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2. Patients should have progressive disease following previous therapy, which must include anthracyclines, taxanes and therapy with trastuzumab in the metastatic setting.

Safety Considerations and Side Effect Management with Lapatinib (Tyverb[®]) and capecitabine.

Annie Young, Nurse Director, 3-Counties Cancer Network (Gloucestershire, Herefordshire and South Worcestershire, UK). Past-president UK Oncology Nursing Society. Paz Fernandez, Institut Català Oncologia ICO, Barcelona, Spain

Empowerment is a primary objective of patient education, which is the cornerstone of the safe administration of oral anti-cancer drugs. Topics that the patient needs to be educated upon include potential and anticipated side effects; how to monitor them as and when they occur, what to do and who to call in the case of their happening. Nurses therefore need to be

able to confidently and competently explain how the prescribed drug works, discuss the benefits of the treatment; how the drug should be taken; the drug schedule; do's & don'ts associated with the regimen including what to do if tablets are missed, or inadvertently overdosed.

Questions you may be asked about lapatinib and capecitabine:

What should I do if forget to take my tablets?

If it is still the same day, take your lapatinib tablets as soon as you remember. Do NOT double the dose the next day. If capecitabine dose is missed (e.g. morning dose), take next dose as usual (do not double up). Remember to inform the cancer unit.

What if I missed a whole day?

Take the usual dose of lapatinib (or capecitabine) on the day after the missed day at the usual time(s). Remember to inform the cancer unit.

What if I am sick after taking my tablets?

Do not take a second dose to make up for the vomited dose. Take next dose as normal when due. If vomiting continues, contact the cancer unit.

What should I do if I get diarrhoea while taking lapatinib?

If diarrhoea occurs it usually happens during the first week or so but can happen at any time during treatment. It is usually mild or moderate, but can be severe in some cases. Most people with diarrhoea should be able to continue their treatment with appropriate management. If experiencing diarrhoea or a change in your normal bowel pattern, inform the cancer unit.

What should I do if I get a rash while taking lapatinib?

Rash is a very common side-effect of taking lapatinib. It usually develops within the first 2 weeks of treatment. The rash will usually improve or disappear after a few weeks. Most people who develop a rash are able to continue their treatment. If a rash develops, or if your skin feels dry, itchy or painful, inform your doctor or nurse.

Management of diarrhoea associated with lapatinib + capecitabine

Early identification is critical for optimal management of this embarrassing and distressing side effect, so it is important that nurses both find ways to encourage patients to talk freely about this symptom in order to help them as quickly as possible and undertake a rigorous assessment. The diarrhoea triggered by targeted therapies is due to damage of the epithelium in the colon due to the presence of the EGFR receptor in this region. As this damage is repaired, the body recovers and for this reason the symptom experience is of short duration.

Evaluation

It is important to evaluate patients for disorders that may dispose them to diarrhoea, such as surgical shortening of the bowel, concurrent non-malignant bowel disorders, or prior bowel irradiation. The assessment and record of medications that may induce diarrhoea, such as antibiotics, should also be completed.

The patient's usual bowel routine should be assessed in order to understand what their normal state is and record the baseline measure. Subsequent grading can be monitored against readily available and utilised Common Toxicity Criteria, such as the North American NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Grade	Measure
1	< 4 stools per day more than baseline
2	4-6 stools per day more than baseline. Not interfering with daily routine.
3	> 7 stools per day. IV fluids. Needs health professional support. Requires hospitalization for complications.
4	Life threatening consequences e.g. haemodynamic collapse. Potential for electrolyte imbalance or similar. Requires immediate attention.
5	Death – extremely rare

Management guidelines based on those developed by the American Society of Clinical Oncology (ASCO)⁹ may be followed on diarrhoea occurrence with lapatinib treatment.

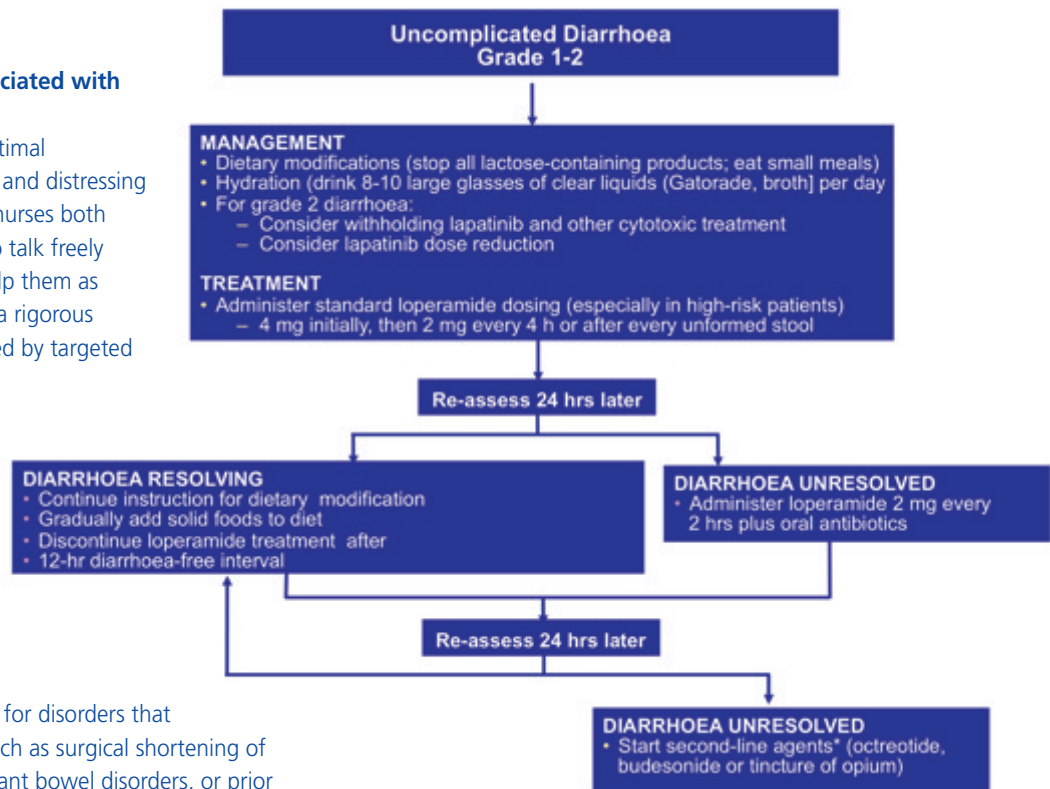


Figure 1. Uncomplicated Diarrhoea

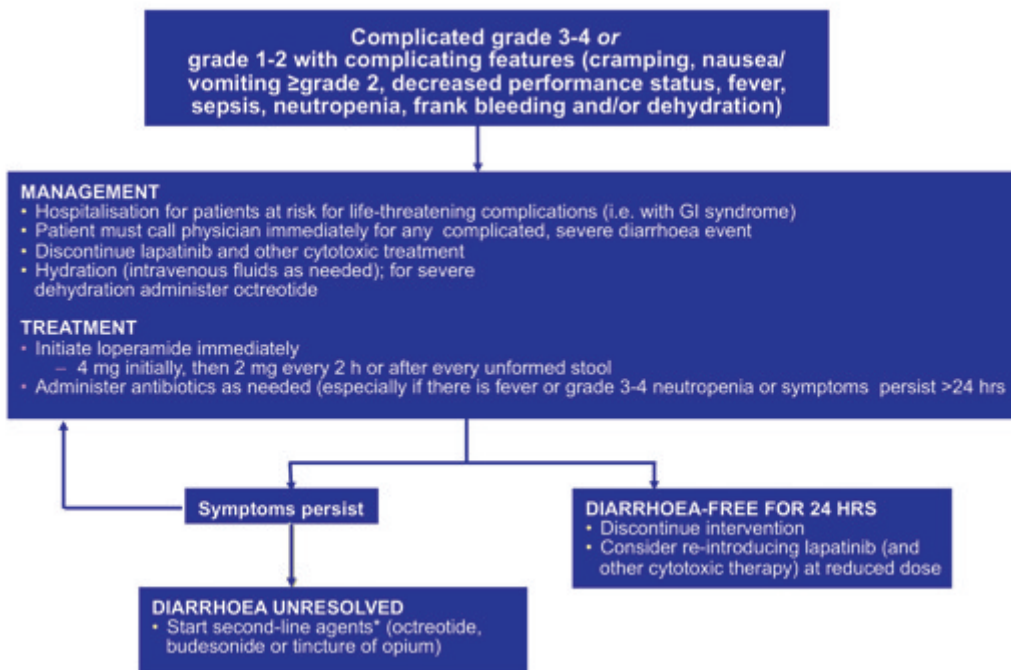


Figure 2. Complicated Diarrhoea

In a pooled analysis of eleven clinical trials of patients receiving lapatinib and/or capecitabine (n = 1,811), diarrhoea occurred in around 55% of patients and was mainly mild and that it tended to last around 5 days¹⁰. Most (92%) diarrhoea events were grade 1 or 2. The majority (85%) of patients required no interruption of therapy or dose adjustment; 2% discontinued treatment because of diarrhoea. Patients who required intervention responded to standard anti-diarrhoeal management (e.g. loperamide). In more severe cases, management included hydration and use of antibiotics. Women are more likely to suffer from diarrhoea than men because of the physiology of their gut; older women will suffer a worse experience than younger women.

Management of skin rash associated with lapatinib + capecitabine

A rash is an obvious side effect and many patients will be sensitive about their appearance, particularly if they experienced hair loss during their initial chemotherapy. Rash is a common side effect of drugs that target the ErbB1 receptor.¹¹

Among lapatinib-treated patients across several trials (n=1,417)¹², skin events were reported by 50% treated with lapatinib monotherapy; 70% with lapatinib + capecitabine; 76% with lapatinib + paclitaxel. The majority of events were of low-grade severity (Grade 1 or 2); there were no Grade 4 events. Events tend to present early in the course of treatment and are usually self-limiting (median duration 29 days).

The correct term for the rash is ‘papulopustular rash’ or ‘pustular eruptions’. The rash may resemble seborrhoeic dermatitis, folliculitis or acneiform drug eruption and it is commonly, (though

technically incorrectly), called an acne-form rash because it is similar in initial appearance to acne vulgaris. However, it is not the same since the rash is not associated with the same clinical or histological characteristics, such as the presence of comedones (“blackheads”). Nevertheless, for women experiencing metastatic breast cancer, the visibility of this rash and obvious further change to their body image may be quite upsetting and worrying.

The papules are small, rounded, elevated lesions in the skin. They tend to be smaller than half a centimetre diameter. A pustule is a collection of purulent exudates in the top

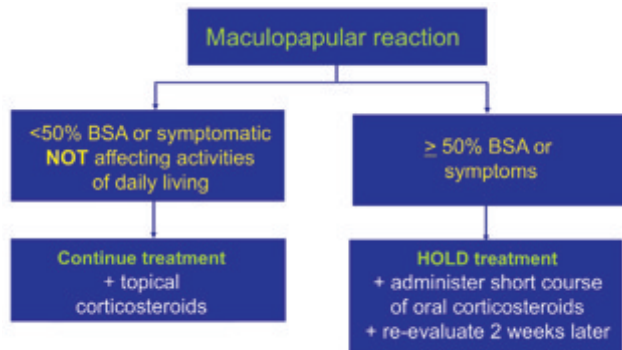
layer of the skin and the epidermis, or beneath it in the dermis. Pustules frequently form in sweat glands or hair follicles. The papulopustular rash commonly affects areas such as the face, the upper back and the V-shaped open neckline area of the chest.

The CTCAE grading gives a common standard to describe the severity of the rash.

CTCAE grading	
Grade 1	Macular or papular eruption or erythema without associated symptoms
Grade 2	Macular or papular eruption or erythema + itching / other associated symptoms. Local desquamation. Covering <50% BSA
Grade 3	Severe. Confluent lesions, or vesicular eruption; desquamation covering >50% BSA
Grade 4	Generalised rash, deep ulcerations, exfoliative or bullous dermatitis
Grade 5	Death

Nurses should perform a skin examination (scalp, radiated areas, hair, nails and oral/genital mucosa) and identification of skin type at baseline and perform follow-up dermatological assessments every 4 weeks throughout treatment or until an adverse reaction appears; after a dermatological event perform skin examinations at every visit until one month after resolution. This will necessarily mean that nurses need to be conversant with the anatomy and physiology of the skin and be able to articulate their findings in language appropriate to this aspect of practice. Patients should be encouraged to avoid exposure to sunlight and apply

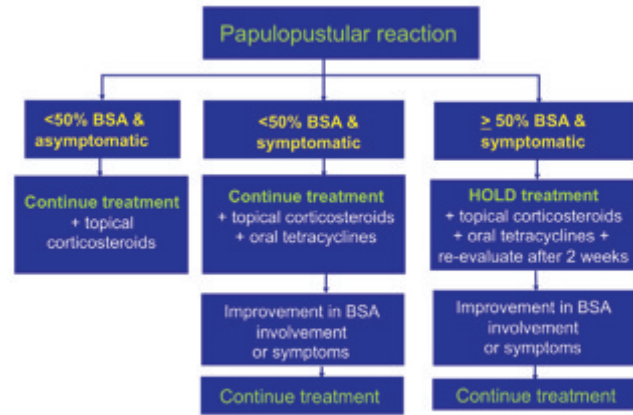
broad spectrum sunscreens (containing titanium dioxide or zinc oxide) with an SPF ≥ 15 . A full body skin examination should be performed on any patient who displays signs or symptoms of dermatological disease.



Guidelines developed by GSK based on Moy & Goss. *Oncologist* 2007; 12: 756-65

Fig 3, management of maculopapular reaction

There are no clear evidence-based treatment options for management of lapatinib-associated rash, however see Figs 3 and 4 for management guidelines derived from one study¹¹. The management of mild rash is relatively simple and may include the application of topical corticosteroids, although there is not consensus for this decision. No discontinuation of treatment is required for mild rash but, if the rash is severe and covering more than 50% of the body surface area or symptomatic, the treatment may be suspended and a short course of oral corticosteroids prescribed and the effect reviewed after 2 weeks. Patients with extensive or persistent skin involvement should be referred to a dermatologist.



Guidelines developed by GSK based on Moy & Goss. *Oncologist* 2007; 12: 756-65

Fig 4 Management of papulopustular reaction

Taken as a whole, side effects with this combination of treatments are less severe than with standard chemotherapy. As always, the nursing contribution to side effect management can make a big difference to the patient experience and quality of life that they will gain from these new therapeutic modalities. In particular, effective communication with patients and efficient education of how to monitor for side effects will be especially important in helping them to get the best from their treatment. Most cancer patients wish to be involved in decision making and are entitled to be treated with dignity and respect - a proactive approach to symptom management will help patients and their carers achieve this.

Nursing considerations for oral agents for cancer.

Sultan Kav, Faculty member at Baskent University, Faculty of Health Sciences, Department of Nursing, Ankara, Turkey.

We all want to see our patients' experience of their cancer and its treatment improve; the attraction of an oral medication is obvious. Administering IV chemotherapy is costly in staff time, clinic space and equipment. It is habitually inconvenient and worrying for patients, often associated with long journeys to hospitals, lengthy waiting times etc. Assuming efficacy and toxicity are equal, it has been shown that patients prefer oral therapies to IV as this reduces disruption to daily schedules, and enables a better quality of life¹³. Nevertheless there are many things that we need to consider for the whole process to be safe and to ensure the best possible outcome for the patient.

Oral medication is associated with a degree of non-compliance. Reasons given for poor adherence to oral anti-cancer agents include a lack of information about the treatment; the perception of the drug's influence over their disease experience and a dislike of certain

unbearable aspects of treatment e.g. unpleasant side-effects¹⁴.

A patient's beliefs may be influential in their decision about whether or not to continue with treatment. Providing support beyond the initial consultation, based on open and honest dialogue combined with a firm, friendly and therapeutic relationship is an important factor in managing such essential outpatient-based services. Other straightforward suggestions for improving adherence include follow up via telephone links; consultations at key points in timeline of patients treatment; involving the support of a third party, such as a carer; informing the patient about reliable and appropriate patient support groups or other voluntary and non-statutory organisations that can help. Even advocating the use of simple measures such as diaries, timers, or post-it notes which serve to remind the patient to take their medication to time could be a useful nursing intervention. In order to make this a positive and valuable treatment option for the long term, nurses will play a vital role in supporting patients for optimising successful outcomes.

A teaching tool for patients receiving oral agents for cancer has been developed by MASCC's professional education study group and can be found at www.mascc.org/mc/page.do?sitePagelId=89760¹⁵.

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Summary

Breast cancer remains the leading cause of cancer-related mortality in European women¹. ErbB2-positive breast cancer accounts for 20 – 30% of invasive breast carcinomas and is a particularly aggressive form of the disease with a poor prognosis³. Knowledge of how intracellular processes are controlled in ErbB2-positive breast cancer has led to the development of targeted therapies which block key signal transduction pathways. Trastuzumab (Herceptin®) is a humanised monoclonal antibody that acts on the extra cellular domain of the ErbB2 receptor and is a crucial component of therapy for ErbB2-positive breast cancer. Lapatinib (Tyverb®) is the first oral

tyrosine kinase inhibitor licensed for use in ErbB2-positive breast cancer and has been shown to target both the EGFR and ErbB2 receptor kinase domains inside the cell.

The main side effects of the lapatinib + capecitabine combination are diarrhoea and rash. Taken as a whole, side effects with this combination are less severe than with standard chemotherapy. Nurses need to be able to explain to patients how their prescribed treatment works, discuss the benefits of the treatment, how to monitor for any side effects and what to do if they occur. Management and education of patients receiving oral anti-cancer therapy needs to be especially thorough to ensure that patients get the best from their treatment. The importance of the nursing contribution for this cannot be underestimated.

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Prescribing Information

Abbreviated Prescribing Information (Please refer to full SmPC before prescribing)

Tyverb®(lapatinib) 250mg film-coated tablets. Each tablet contains 250mg lapatinib as ditosylate monohydrate. **Indications** In combination with capecitabine for treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting. **Dosage and administration** Only to be initiated by physician experienced in use of anti-cancer agents. **Lapatinib:** 1250mg (5 tablets) once daily continuously. Taken at least one hour before, or at least one hour after food. Standardise administration in relation to food intake. **Capecitabine:** 2000 mg/m² /day taken in 2 doses 12 hours apart on days 1-14 in a 21-day cycle. Taken with food or within 30 mins after food. **Renal impairment:** No lapatinib dose adjustment necessary in mild to moderate renal impairment. Caution advised in severe renal impairment as no experience of lapatinib in this population. **Hepatic impairment:** Discontinue lapatinib if changes in liver function are severe and do not retreat patients. Insufficient data available to provide a dose adjustment recommendation. Use with caution in moderate to severe hepatic impairment due to increased exposure to product. **Elderly:** Limited data in patients ≥ 65 years. **Paediatrics:** Not recommended. **Dose delay and dose reduction** **Cardiac events:** Discontinue lapatinib in patients with symptoms associated with decreased LVEF that are NCI CTCAE grade ≥ 3 or if LVEF drops below institution's LLN. May be restarted at 1000mg/day after ≥ 2 weeks and if LVEF recovers to normal and patient is asymptomatic. **Interstitial lung disease/pneumonitis:** Discontinue lapatinib in patients who experience pulmonary symptoms that are NCI CTCAE grade ≥ 3. **Other toxicities:** Consider discontinuation or interruption of lapatinib dosing if patient develops toxicity that is NCI CTCAE grade ≥ 2. Can be restarted at 1250mg/day when toxicity improves to ≤ grade 1. If recurs, restart lapatinib at 1000mg/day. Consult capecitabine SmPC for guidance on dose delay and dose reduction recommendations for capecitabine. **Contra-indications** Hypersensitivity to active substance or excipients. Refer to capecitabine SmPC for relevant contraindications and safety information. **Special Warnings and Precautions** Decreases in LVEF reported. Caution advised if lapatinib given to patients with conditions that could impair LVEF. Evaluate LVEF in all patients prior to starting treatment to ensure baseline LVEF within institution's normal limits. Evaluate LVEF during treatment to ensure it does not decline to unacceptable level. Hepatotoxicity has occurred (may rarely be fatal). Monitor liver function before initiation of treatment and monthly thereafter or as clinically indicated; Pulmonary toxicity including interstitial lung disease reported. Monitor for symptoms of pulmonary toxicity; Diarrhoea including severe diarrhoea reported. Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases may require oral or i.v. electrolytes and fluids, and interruption/discontinuation of

therapy. **Interactions** Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8. Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. Avoid grapefruit juice during lapatinib treatment; Avoid concomitant treatment with inducers (incl. St. John's Wort) and strong inhibitors of CYP3A4, and with medical products with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8; Avoid concomitant use of substances that increase gastric pH as lapatinib solubility and absorption may decrease. **Pregnancy and lactation** No adequate data on use in pregnant women. Not to be used unless clearly necessary. Contraception advised; Not known whether lapatinib excreted in human milk. Breastfeeding should be discontinued. **Effects on ability to drive and use machines** No studies conducted. Deterioration effect cannot be predicted from pharmacology of lapatinib. **Undesirable effects** Following adverse reactions reported in association with lapatinib + capecitabine therapy: **Very common:** Diarrhoea (may lead to dehydration), nausea, vomiting, dyspepsia, stomatitis, constipation, abdominal pain; Rash (including dermatitis acneiform), dry skin, PPE; Anorexia; Fatigue; mucosal inflammation; Pain in extremity; back pain. **Insomnia.** **Common:** Decreased LVEF; Nail disorders including paronychia **Headache;** Hyperbilirubinaemia, hepatotoxicity. **Uncommon:** interstitial lung disease/pneumonitis. **Rare:** Hypersensitivity reactions including anaphylaxis. **Specific events:** **Decreased LVEF:** Reported in ~1% of all patients receiving lapatinib across clinical programme and asymptomatic in > 90% cases. Symptomatic LVEF decreases observed in ~ 0.1% of patients on lapatinib monotherapy. Symptoms included dyspnoea, cardiac failure, palpitations. LVEF decreases reported in 2.5% of patients on lapatinib + capecitabine vs. 1% for capecitabine alone. **Diarrhoea:** Occurred in ~ 65% of patients on lapatinib + capecitabine. Most cases grade 1 or 2 and did not result in discontinuation of lapatinib. **Rash:** Occurred in ~ 28% of patients on lapatinib + capecitabine. Generally low grade and did not result in discontinuation of lapatinib. **Overdose** No specific antidote. Haemodialysis not expected to be effective method of elimination as lapatinib is not significantly renally excreted and is highly bound to plasma proteins. **Marketing authorisation (MA) no.** EU/1/07/440/001 and EU/1/07/440/002 **MA holder** Glaxo Group Limited, Berkeley Avenue, Greenford, Middlesex UB6 0NN. **Legal category** POM. TYV0110/105/1 January 2010.

Adverse events should be reported. Reporting forms and information can be found at: www.yellowcard.gov.uk GlaxoSmithKline encourages healthcare professionals to report adverse events, pregnancy, overdose and unexpected benefits to the company on 0800 221 441.

Further contact information is available from <http://www.gsk.com/contactus.htm> or email Oncologywebmaster@gsk.com

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