

# Nursing management approaches with a new targeted therapy for ErbB2-positive breast cancer



A GlaxoSmithKline-sponsored satellite symposium was held on Friday 28th March, 2008, at the recent 6th EONS Spring Convention in Geneva, Switzerland: 'New Insight: New Outlook'.

This symposium was developed to describe and discuss the important role of an investigational cancer therapy in the treatment of ErbB2 positive breast cancer, and the vital role of the nurse in the care of patients receiving such treatments. Almost 200 delegates attended the symposium and were able to actively participate in interactive votes, recorded in real time and relayed onto the auditorium screen, in response to questions posed by the various speakers.

## Introduction

*Jan Foubert, Dean, Faculty of Healthcare, and a Senior Lecturer in Nursing and Midwifery at the Erasmushogeschool, Brussels, and Executive Director of EONS*

Breast cancer is the most prevalent cancer in women worldwide, with more than 1.1 million worldwide diagnosed and living with the disorder, which is more than any other type of cancer except skin malignancies.<sup>1</sup> It is estimated that 1 in every 12 women will develop breast cancer at some point in their lifetime. Breast cancer is also the leading cause of cancer death among women worldwide; 1 in 28 women will die of breast cancer.<sup>2</sup>

There is a considerable geographical variation of breast cancer incidence across the globe; the highest incidence figures are seen in the Western world with significantly lower rates seen in poorer, developing countries.<sup>3</sup> In Europe, the highest incidence is seen in Western and Northern European countries, such as Germany, France, and the United Kingdom; the lowest incidence is experienced in Southern and Eastern European countries such as Latvia and Lithuania.<sup>2</sup> Overall, the risk of developing breast cancer in Western Europe has been suggested to be 60% greater than those populations living in Eastern Europe.<sup>3</sup>

Table: Prevalence of Breast Cancer in the European Union (Data from Globocan 2002)

Country	1-year prevalence
Germany	54,424
France	41,988
UK	37,954
Italy	36,647
Spain	15,753

Although the prevalence of breast cancer has progressively and steadily risen over the past few decades, from 1990 to 2002 the breast cancer death rate decreased by 2.3% per year.<sup>2</sup> This is partly due to the development of methods of detecting malignant lesions earlier, such as the now well-established breast screening programmes, and also the technological and medical advances in treatment and supportive care, such as targeted therapies. For many women, breast cancer may now be considered a chronic illness, and patients have to learn to live with their disease. Survivorship issues will become an increasingly important area for nursing care and research development. Nevertheless, cancer is still now equated with a range of emotional experiences, many negative such as fear, anxiety, anger and despair all of which may influence the information needs, perceptions, comprehension and retention. As breast cancer is more commonly seen in women over the age of 50, concomitant co-morbidities may also compromise

*The production of this article has been supported by GlaxoSmithKline*

NEW INSIGHT  NEW OUTLOOK

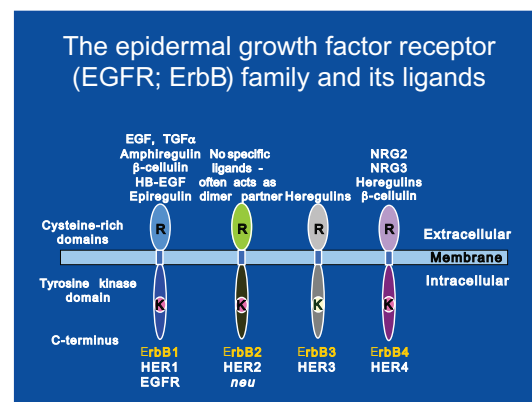
well-being. Nurses need to be able to not only understand and manage all these factors, assessing the individual information needs of each patient and their family, but also need to be able to provide appropriate counsel, advice and education to provide relief from distress, both physical and psychological. The need for nurses to be able to understand the science behind the modern therapies, in order to adequately answer questions is apparent. To meet this need, in part, the delivery of contemporary cancer nursing services has developed with many innovative changes being seen, such as the shift to chemotherapy administration in the home or mobile units visiting more remote areas. There have also been changes in the way therapies are delivered, with a growth in oral

formulations of treatment and development of other non-intravenous delivery systems, which traditionally required in or out-patient care. This has necessitated new ways of teaching patients to ensure compliance and safety. And finally, there have been changes to the way that services are delivered, such as nurse led clinics and nurse prescribing, especially in the UK and Nordic countries. This article provides an insight into some of the elements influencing nursing management with a new targeted therapy for ErbB2-positive (ErbB2+) breast cancer, including an appreciation of the research into the drug therapy, the patient experience and participation in care and specific symptom management issues.

## Targeted therapy in breast cancer

*Professor John Crown, consultant medical oncologist, St Vincent University Hospital, Dublin, Eire.*

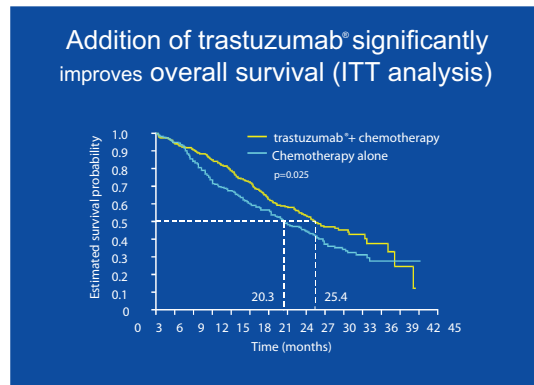
We live in a very exciting time in oncology, where we may now be seeing the beginning of the end of the chemotherapy era and the transition to the age of molecular therapy. This evolution is necessary because, in spite of the major and meaningful advances made with cytotoxic chemotherapy, especially in the adjuvant treatment of early stage breast cancer, where numerous lives have been saved and prolonged, chemotherapy is essentially an inelegant treatment modality. It arose from research into chemical warfare and, because of the non-specific nature of chemotherapy; it is still associated with formidable side-effects. Thankfully, whilst the necessary clinical research and trials into chemotherapy that gave us the medical advances to date were being undertaken at the bedside, a parallel process of laboratory based research was developed. These two branches are merging into a seamless translational research initiative where laboratory research is increasingly presenting new molecules for clinical application and clinical staff are providing new observations and tissue materials that help with diagnostic and prognostic evaluation and improvements in therapy. This approach has caught the imagination of the public and imatinib (Glivec®), a tyrosine kinase signal transduction inhibitor, utilized firstly in the treatment of chronic myeloid leukaemia, was popularly heralded as the first drug to revolutionize modern cancer treatment. Breast cancer came a close second, where most of the early interest in the utility of molecular therapies in breast cancer revolved around the HER-2 (Human Epidermal Growth factor Receptor 2), ErbB or epidermal growth factor family of trans-membrane receptors. Some of these receptors have well identified ligands (binding molecules) whilst the role of others remains obscure.



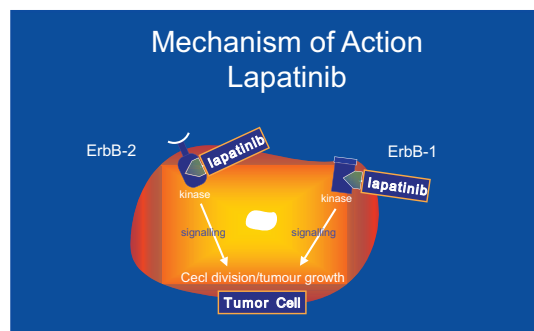
The two receptors most therapeutically exploited are the ErbB1 (EGFR) and ErbB2 (HER2). The ErbB1 receptor has been targeted by a number of different drugs, most successfully in colorectal cancer; however, attempts to target ErbB1 in breast cancer have been less successful to date. Nonetheless, one has to ask whether if there had been more caution and smarter testing and trials of these drugs on targeted patients, would we be seeing more of a role and use of these drugs in breast cancer?

The ErbB2 system has been much more successfully targeted in breast cancer. An altered, amplified ErbB2 gene predicts for a worse prognosis – the disease is more aggressive and tends to recur and relapse more quickly. Extraordinarily, the development of a molecularly targeted response, the drug trastuzumab (Herceptin®), and a rational approach to translational research, evidenced in a first generation randomized trial which compared chemotherapy alone versus chemotherapy and trastuzumab resulted in much improved results; the general and widespread clinical application of an appropriate therapy for breast cancer; and an invigoration of the whole field of cancer research. A surprising result of the ErbB2-antagonism story was the development of cardiotoxicity in patients receiving trastuzumab for

metastatic breast cancer, where it was found that up to 7% of patients receiving this agent might experience this effect and this incidence figure was increased in patients who had received concomitant anthracycline and cyclophosphamide therapy (AC).<sup>4</sup>



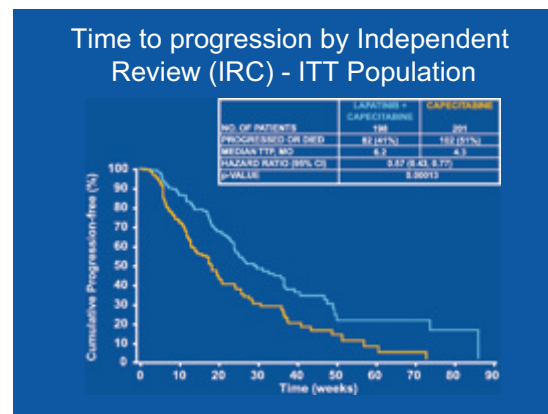
Subsequent American and European trials<sup>5</sup> revealed that trastuzumab had a valuable role to play in breast cancer management (see slide above). Further confirmation of the validity of trastuzumab was obtained from the Breast Cancer International Research Group (BCIRG) 006 trial, where treatment with AC followed by docetaxel was compared with AC followed by docetaxel plus trastuzumab, and with docetaxel in combination with carboplatin and trastuzumab, where 2-year interim results showed a trend toward an overall survival benefit.<sup>6</sup> Lapatinib (Tyverb<sup>®</sup>) is a small molecule, dual tyrosine kinase inhibitor of epidermal growth factor receptor ErbB1 (EGFR) and ErbB2 (HER2), where its action against ErbB1 may theoretically augment the anti-ErbB2 effect through complex interactions between those receptors. Most people would now seem to believe that most of the activity for lapatinib is going to be in the ErbB2 positive population of patients.



The first phase III randomized trial of lapatinib was presented recently in European and American meetings and subsequently published.<sup>7</sup> Follow-up data from the trial demonstrated that the independently-assessed time to progression (TTP) – the period of time during which the cancer is not getting any worse – was statistically

significantly longer for patients treated with lapatinib + capecitabine than for those treated with capecitabine alone (6.2 months vs. 4.3 months [HR 0.57 (95% CI, 0.43 – 0.77; p<0.001)]) in women with progressive ErbB2+ metastatic breast cancer, all of whom had been previously treated with anthracyclines, taxanes and trastuzumab.<sup>8</sup>

A statistically significant improvement in investigator-assessed TTP and response rate, following the lapatinib and capecitabine arm was also seen.



As a result of these findings, it was decided that the study should be suspended and patients on the control arm offered access to treatment with lapatinib if they so wished. Lapatinib has recently received EMEA approval for this indication, for use with capecitabine, in patients with ErbB2+ advanced metastatic breast cancer who have received prior treatment with anthracyclines, taxanes and trastuzumab in the metastatic setting.

Trastuzumab is a critically important drug. It is an antibody, the production of which is technically difficult and it is hoped that the long-term development of smaller, rational molecules that target the receptor from the inside of the cancer cell and which may be administered as tablets will assume an important niche. These molecules may also confer an additional therapeutic advantage. Some antibodies, like trastuzumab, do not cross the intact blood-brain barrier and, as a result, patients who are treated with trastuzumab may relapse with metastatic lesions in their brain. In the report of updated efficacy, an exploratory retrospective analysis showed a statistically significant advantage for the lapatinib + capecitabine arm of the study, where 4 patients (2%) versus 13 patients (6%) in the capecitabine arm had CNS disease as part of their first progression (p=0.045). This suggests lapatinib reduces the risk for CNS progression and is the basis of ongoing research in this area. In addition, the lapatinib plus capecitabine combination appears to be associated with a low incidence of cardiac events. In this study, lapatinib plus capecitabine were well tolerated and the majority of adverse events were mild

to moderate. Diarrhoea often occurs in patients receiving capecitabine; the nursing management of which is covered in the following section. Lapatinib increased the frequency of mild (grade 1/2) diarrhoea by about 20%. Rash was also more common with the combination but lapatinib did not otherwise appreciably alter the toxicity profile of capecitabine.<sup>8</sup>

The notion of attacking the ErbB2 receptor in two different ways, with trastuzumab from the outside and lapatinib

from the inside, is supported by laboratory data that suggests that a combination may be a more effective means of inhibiting the growth of ErbB2+ breast cancer cells and a number of trials are presently examining this prospect.

We are winning the war on breast cancer; the mortality rate for breast cancer is falling and falling dramatically, and it appears to be going down the most in countries that are taking it seriously. We have much to be proud of.

## Side effect management of Lapatinib

*Carole Farrell, Nurse Clinician, Christie Hospital NHS Foundation Trust, Manchester, UK*

The management of breast cancer is becoming increasingly complex with new and different ways of working and new complicated treatments to work with, particularly targeted therapies; however, it is important for oncology nurses to keep not only themselves up to date but also their patients so that they may make important informed treatment choices.

Two of the predictable side effects associated with lapatinib, and when combined with treatment such as capecitabine, are diarrhoea and rash.

It is important that we remember the subjective nature of symptoms and that perception differs between patients and between patients and professionals.

Lapatinib is associated with mainly mild episodes of diarrhoea (grade 1-2) but approximately half of all treated patients will experience this symptom.<sup>9</sup> When lapatinib is combined with capecitabine there is a reportedly greater incidence of diarrhoea (approx 60%) but the severity of the diarrhoea is similar to that associated with each drug alone. The evidence from clinical trials would suggest that the incidence of severe (grade 3) diarrhoea is approximately 12% and grade 4 is 1%. Therefore, whilst the occurrence is generally mild and predictable, nurses should be aware that there is still an important risk for particularly vulnerable patients, such as those with neutropenia, or severe diarrhoea with life-threatening complications.

The response to an interactive question indicated that 56% of the delegates worked in institutions that had guidelines for the management of cancer-treatment associated diarrhoea.

Some of the most important elements for managing this symptom are the comprehensive education of all staff,

medical and nursing, and clear written protocols and guidelines that are translated into clear clinical patient management. This includes a planned schedule for patient evaluation, review and guidelines for dose reductions. A particularly important element is clear guidance for the content for educating and informing the patient about oral treatments. When patients receive intravenous therapies the patient may be seen by specialist nurses and doctors who explain all aspects of the treatment schedule but this may not necessarily be the same for patients receiving oral treatments, unless the patient is part of a clinical trial. A thorough assessment of the patient's experience of diarrhoea is essential (see table below)

- Obtain history of onset and duration of diarrhoea
- Describe number of stools and composition
- Assess for additional symptoms to rule out risk for:
  - Sepsis
  - Bowel obstruction
  - Dehydration
- Dietary profile
- Assess grade of symptoms (WHO CTC criteria)
  - Grade 1 < 4 stools per day more than baseline
  - Grade 2 4-6 stools per day more than baseline. Not interfering with Activities of Daily Living
  - Grade 3 ≥ 7 stools per day. IV fluids. Requiring hospitalization. Interfering with ADL
  - Grade 4 Life threatening consequences e.g. haemodynamic collapse




*Guidelines developed by GSK based on Benson et al. J Clin Oncol 2004; 22:2918-26*

The majority of cases of diarrhoea with this treatment regimen will be uncomplicated Grade 1-2 diarrhoea and so the management is straightforward with simple measures such as dietary modifications, stopping all lactose-containing products, eating small regular meals and maintaining hydration. For grade 2 diarrhoea, treatment may be suspended and patients are advised to self-administer loperamide (4 mg initially, then 2 mg after every unformed stool). If after 24 hours the diarrhoea resolves, dietary modification may be continued and solid foods may be gradually added to the diet. Loperamide would be stopped after a 12 hour diarrhoea-free interval. In cases of Grade 3 or 4 diarrhoea, the patient should be medically reviewed and admitted to hospital if experiencing life-threatening complications. Lapatinib and capecitabine should be discontinued and adequate hydration maintained, including IV fluids if indicated.

#### Rash

There are two discrete types of dermatological reaction associated with lapatinib, maculopapular and papulopustular rashes. 60-70% of patients can have a rash with EGFR inhibitors, usually occurring within the first 2 weeks of treatment.<sup>10</sup> and spontaneously resolving during

treatment or after interruption / cessation of treatment. 15% of patients on capecitabine and 28% on lapatinib + capecitabine experienced a rash<sup>9</sup> but for the majority of patients most rashes are mild (grade 1-2); 1% are grade 3. The rash may resemble seborrhoeic dermatitis, folliculitis or acneiform drug eruption but is different from acne vulgaris. Nevertheless, for most women experiencing metastatic breast cancer, the visibility of this rash and obvious further change to their body image may be quite distressing. The rash is graded according to the Common Terminology Criteria (see table below). The management of mild rash may include the application of topical corticosteroids but no discontinuation of treatment 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. General skin care measures are advisable, such as the use of sun protection and hypo-allergenic make up and emollients for dry skin. Colloidal oatmeal lotion may also be effective. In severe cases of extensive skin involvement, referral to dermatologist may be appropriate. Antibiotics, such as topical clindamycin 1% gel / benzoyl peroxide 5% gel or oral antibiotics e.g. tetracycline 250mg QDS or minocycline 100mg BD may be appropriate for pustular rash.

Grade of Rash	Presentation	Appearance
<b>Grade 1</b>	Macular or papular eruption without symptoms	
<b>Grade 2</b>	Same lesions. Also itching / other symptoms. Covering <50% BSA	
<b>Grade 3</b>	Confluent lesions, severe eruption covering >50% BSA	
<b>Grade 4</b>	Deep ulcerations, exfoliative or bullous dermatitis	

## Management of Emesis and Hand-Foot Syndrome with oral capecitabine

Gill Donovan, Lead Breast Oncology Nurse Specialist, Cancer Care Cymru

Chemotherapy is the mainstay of metastatic breast cancer treatment with over 60% of cancer patients in Europe currently receiving this treatment modality. Patients would generally prefer oral chemotherapy provided it is as efficacious as the same IV chemotherapy.<sup>11</sup> Whilst capecitabine is not usually associated with high levels of chemotherapy induced nausea and vomiting (CINV) it is nonetheless worth remembering that in 2006, 675,000 patients across Europe received highly or moderately emetogenic chemotherapy in Europe, and many appear to be under-treated or are not given the right type of prophylactic anti-emetics. Inadequate CINV control has serious negative effects on the lives, health and well-being of patients causing some patients deciding to cease their treatment. It may result in dose reduction, which in turn could affect the efficacy and outcome of treatment. For some patients, the fear that their treatment may be stopped if they report adverse events may mean their symptoms are not reported, with ultimately serious consequences for them, such as dehydration. Nausea and vomiting may be graded according to available scores and guidelines (see chart below).

Grade of N&V	Severity and Effect on food intake	Frequency
<b>Grade 1</b>	<b>Mild</b> No significant effect on food intake	1 episode in a 24 hour period
<b>Grade 2</b>	<b>Moderate</b> Food intake significantly decreased but able to eat intermittently	2-5 episodes in a 24 hour period
<b>Grade 3</b>	<b>Severe</b> Unable to eat	6-10 episodes in a 24 hour period
<b>Grade 4</b>	<b>Life threatening</b> May be the need for parenteral support	>10 episodes in a 24 hour period

(Vomiting grading adapted from National Cancer Institute of Canada Common Terminology Criteria, 1994)

Nurses have a key role in managing these symptoms, assessing the patient and reporting their findings to their medical colleagues.

The four emetic risk groups (MASCC, 2008) are tabulated below and it is important to note that the patients being treated for breast cancer are often falling into the moderate classification

<b>High</b>	Risk in nearly all patients (> 90%)
<b>Moderate</b>	Risk in 30% to 90% of patients
<b>Low</b>	Risk in 10% to 30% of patients
<b>Minimal</b>	Fewer than 10% at risk

(Multinational Association of Supportive Care In Cancer-Antiemetic Guidelines -Latest Update: March 2008, based on the Consensus Conference on Antiemetic Therapy conducted 2004)

Recommendations regarding the CINV have been made (see table below), with a comprehensive consensus on the use of 5-HT3 antagonists and corticosteroids.

	Acute CINV	Delayed CINV
<b>ASCO</b>	5-HT3 antagonist + dexamethasone + aprepitant	Dexamethasone + aprepitant
<b>MASCC</b>	5-HT3 antagonist + dexamethasone + aprepitant	Dexamethasone + aprepitant
<b>ESMO</b>	5-HT3 antagonist + corticosteroid + aprepitant	Corticosteroid + aprepitant
<b>NCCN</b>	5-HT3 antagonist + dexamethasone + aprepitant ± lorazepam	Dexamethasone + aprepitant ± lorazepam

Clinical observation and results from a phone back service over a 3-year period for patients receiving chemotherapy has suggested that 50% or so of patients taking steroids are suffering steroid-related side effects, which suggests we need to address how we manage this issue in the future.

New agents such as aprepitant are being used though the cost of the drug may be limiting its use.

### Hand-Foot Syndrome

Hand-foot syndrome (HFS) is a very distressing side effect and is not just seen solely with capecitabine, it is frequently seen with cytarabine, fluorouracil, idarubicin and doxorubicin. HFS is one of the most common side effect

of capecitabine and can range from mild to severe where skin, for example finger tips and toes, split. The severity of the phenomenon may be graded according to the WHO definition<sup>12</sup> where grade 1 represents dysaesthesia or paraesthesia and grade 4 desquamation, ulceration and epidermal necrosis.

Grade	Criteria/Definition
1	Dysaesthesia/paraesthesia (Tingling in hands and feet) Erythem
2	Discomfort in holding objects and upon walking, painless swelling or erythema + oedema
3	Painful erythema, swelling of palms and soles
4	Desquamation, ulceration, blistering, severe pain. Complete epidermal necrosis

It is important that nurses check for HFS at every patient visit. This may involve such basic approaches as asking the patient to remove their shoes so that their feet can be examined.

## Compliance and Patient Education for Oral Treatments

*Liesbeth Lemmens, Co-ordinator, Clinical trials- digestive oncology, University Hospitals, Leuven, Belgium*

Oral treatments include chemotherapy and targeted therapies and, whilst there have been some oral chemotherapeutic agents available for more than 50 years, such as chlorambucil (Leukeran®), the increasing number of oral drugs in development would suggest we are entering a new era of oral anticancer therapy. This means that there is going to be a challenge to restructure and reorganize the services that provide care. Oncology nurses are uniquely positioned to educate patients in their treatment needs but this means that nurses themselves must be educated in the issues that influence and determine patient concordance. These include patient-related factors such as the level of their health literacy and health system related factors that may for example influence reimbursement of costs, such as in situations where the UK has nurses that can prescribe medications but Belgium does not.

Oral treatments are associated with their own particular advantages and disadvantages. The advantages include the convenience and flexibility to the patient, they may not require as many admissions or visits to hospital and this may in turn reduce health care costs. Disadvantages include the lack of nursing involvement in the prescribing and dispensing process.<sup>14</sup> Health care costs and burden to

Treatment interruptions and dose modification are the only known methods to effectively manage HFS and there is no adverse effect on the efficacy of the treatment. Evidence for supportive measures are limited and / or conflicting<sup>13</sup> but measures currently being utilised include avoiding friction, and keeping the hands and feet cool. There is some evidence for using Pyridoxine (Vitamin B6) 50mgs three times a day (but not prophylactically). There is some anecdotal evidence for petroleum-ianolin / Urea based ointment and Vitamin E. In summary, the nurses' role is pivotal for the prevention and treatment of HFS. Patient education (what to look for and what to do about it) is central to effective care. Preventative emollient use may have a role. Nursing staff should ensure the patient has telephone access to a key person. Patients should be followed-up (by phone or clinic appointment) and they should be assured that the condition is rarely permanent. A diary, recording drug dosage and associated events may be important in monitoring concordance.

the patient could subsequently rise if they consequently suffered adverse effects through lack of appropriate advice and supervision.

As mentioned before, patients generally prefer oral therapy if efficacy and toxicity are equal. If treatment reduces interference with daily work commitments, reduces time spent travelling and associated costs, it could contribute to a better quality of life.

Factors that increase the likelihood of a patient's agreement or concordance include their individual motivation; the suitability and acceptability of dosing schedule; the complexity of dosing schedules; the timing of a dose in relation to food intake; the experience of side effects and their management; and costs of the treatment and the remedy of any side effects.

Measures that improve the likelihood of concordance include detailed patient education, the use of written information and diaries; and pill boxes and other aide-memoires for medication scheduling.



The literature suggests that relatively simple measures create the retention of information. Efficient education encounters should be no longer than 60 minutes. Patients should be encouraged to bring a relative or good friend to reinforce their knowledge retention. The discussion should be conducted in a private area and written information should be provided. The 'tell me' technique (see chart) can be employed in the patient education process and details the questions that nurses should be prepared to address and patients should be able to answer.

- What is the name of the drug? Is there more than one name?
- What is the mode of action?
- How is it taken? Swallow? Crush? Open?
- When should it be taken?
- Is it safe to take with other drugs, food, herbal supplements? Interactions?
- What if patient misses a dose?
- How to store the drug?
- Are there any side effects?
- What are the costs?
- Who is the contact person (nurse – patient)?

## SUMMARY

The new era of cancer treatment is typified by the progressive 'bench to bedside' promise of more specific targeted therapies, which focus on molecular and cell biology and immunology to help achieve tumour control. Targeting the ErbB2 (HER2) growth receptor, with agents such as lapatinib and trastuzumab, offers one such approach for patients with breast cancer. The expansion of our knowledge and understanding of the science of cancer needs to be matched by an increase in the science and

art of cancer nursing care and, as the speakers in this symposium illustrated, this will require an increase in the knowledge of nurses in clinically relevant details such as the management of the potential side effects such as skin rashes, diarrhoea and hand-foot syndrome. It also necessitates the need for, and ability of nurses to educate and empower patients so that they are not merely the passive recipients of care but partners participating in an agreed, appropriate and individual programme of care.

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## 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/m<sup>2</sup> /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** 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. Detrimental 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; Headache; Hyperbilirubinaemia, hepatotoxicity. **Uncommon:** interstitial lung disease/pneumonitis. 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. **Basic UK NHS Cost** 70 tablet pack £804.30. **Marketing authorisation (MA) no.** EU/1/07/440/001 **MA holder** Glaxo Group Limited, Berkeley Avenue, Greenford, Middlesex UB6 0NN. **Legal category** POM. TYV/PR/08/34299/2. May 2008

Adverse events should be reported. Reporting forms and information can be found at: [www.yellowcard.gov.uk](http://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 information is available from: GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. Leukeran and Tyverb are registered trademarks of the GlaxoSmithKline group of companies. ONC.ARTI/08/36586/1 June 2008