NEW DRUGS/DRUG NEWS
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LAPATINIB DITOSYLATE (TYKERB – GLAXOSMITHKLINE INC.) FOR ADVANCED OR METASTATIC BREAST CANCER

BACKGROUND

Breast cancer is the most common form of cancer among Canadian women; in 2009, an estimated 22,700 women will be diagnosed with the disease and 5,400 will die of it.1 The majority of women diagnosed with breast cancer will have early-stage illness; however, approximately 30% of such patients will eventually develop advanced or metastatic disease.2,3 Unfortunately, metastatic breast cancer is generally incurable and median survival is only two to three years.2 As a result, the main therapeutic goals are palliative, including symptom control, prolongation of survival, and improvement of quality of life.4

The prognosis for those with metastatic breast cancer is influenced by many factors, including tumour overexpression of human epidermal growth factor receptor 2 (HER2; also known as ErbB2), which is present in approximately 20–30% of cases.4 Historically, HER2 amplification has been associated with more rapid tumour growth and a poorer prognosis compared with HER2-normal breast cancers.2,4,5 The recognition of HER2 as a target in breast cancer cells led to the development of the intravenous monoclonal antibody trastuzumab (Herceptin), which changed the way HER2-positive breast cancer is treated.5,6 The recent introduction of lapatinib ditosylate (“lapatinib”; Tykerb – GlaxoSmithKline Inc.) to the Canadian market provides another option for the treatment of breast cancer that overexpresses HER2.

PHARMACOLOGY

Lapatinib is a small-molecule, reversible, selective inhibitor of the intracellular tyrosine kinase domains of human epidermal growth factor receptor 1 (HER1; also known as EGFR or ErbB1) and HER2.7,8 These receptors, and others in the human epidermal growth factor receptor family, are known to mediate tumour angiogenesis, growth factor signalling, proliferation, and metastasis.2

PHARMACOKINETICS

Absorption of lapatinib following oral administration is incomplete and variable (~50–100% coefficient of variation in systemic exposure), with peak plasma concentrations reached approximately four hours post-dose.7 The drug is highly (>99%) bound to plasma proteins, although data indicate lapatinib has good tissue distribution and there is growing evidence to suggest that it penetrates the central nervous system.5,7,8 Lapatinib is extensively metabolized, primarily via cytochrome P450 (CYP)3A4 (~70% of metabolism), with lesser contributions from CYP3A5, CYP2C19, and CYP2C8.7,8 One metabolite is active against HER1 (but not HER2), whereas other metabolites appear to be inactive.8 Studies suggest that roughly 27% of an oral dose is eliminated in feces and less than 2% is eliminated in the urine.7 The half-life following repeated dosing is around 24 hours.8

EFFICACY

The efficacy of lapatinib in the population of patients for whom the drug is officially approved (see Indications, above) was demonstrated in a pivotal phase III study.9,10 The trial was relatively small (n=399 in the updated analysis)10 and employed a randomized, open-label design. Patients were eligible for study inclusion if...
they had HER2-positive, locally advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline and a taxane (at least 4 cycles [2 if progression occurred while receiving therapy], administered concurrently or separately) and trastuzumab (at least 6 weeks of therapy, alone or in combination with chemotherapy). A key exclusion criterion was previous therapy with capecitabine.9

Eligible participants were randomly assigned to receive either combination therapy with lapatinib and capecitabine (lapatinib 1250 mg once daily continuously plus capecitabine 2000 mg/m² [divided bid] on days 1 through 14 of a 21-day cycle) or capecitabine monotherapy (2500 mg/m² [divided bid] on days 1 through 14 of a 21-day cycle). Pre-defined dosage adjustments for both medications were made as necessary for specified drug toxicities. Treatment was continued until disease progression was identified by study investigators or unacceptable toxic effects occurred.9

The primary endpoint of the study was time to progression (TTP), based on blinded evaluation by independent reviewers. Secondary endpoints included overall survival and overall response rate. The analyses of efficacy data were carried out in the intention-to-treat population, comprising all women who underwent randomization.9

Based on the results of a pre-specified interim analysis (n=324) that showed an improvement in TTP for patients receiving lapatinib plus capecitabine (n=163) compared with those receiving capecitabine alone (n=161) (8.4 months vs. 4.4 months, respectively; hazard ratio, 0.49 [95% confidence interval, 0.34–0.71; p<0.001]), the trial was halted. At that time, the overall response rate was 22% (95% CI, 16–29) in the combination-therapy group (35 partial responses, 1 complete response) and 14% (95% CI, 9–21) in the monotherapy group (23 partial responses) (p=0.09); no survival advantage was evident (p=0.72).9

Results of an updated analysis,10 which included an additional 75 patients, confirmed the benefits of combination therapy on TTP (6.2 months vs. 4.3 months for monotherapy; hazard ratio, 0.57 [95% CI, 0.43–0.77; p=0.001]) and overall response rate (23.7% vs. 13.9%; odds ratio, 1.9 [95% CI, 1.1–3.4; p=0.017]). However, there was still no demonstrated advantage for overall survival (67.7 weeks vs. 66.6 weeks; hazard ratio, 0.78 [95% CI, 0.55–1.12; p=0.177]).10

PRECAUTIONS & ADVERSE EFFECTS

The primary warnings and precautions for lapatinib relate to its potential to cause hepatotoxicity, decreased left ventricular ejection fraction (LVEF), QT/QTc interval prolongation, and diarrhea.7 Generally speaking, the drug should be administered with caution to individuals with these conditions or risk factors for them, and all may necessitate interruption or termination of therapy should they occur. In the pivotal clinical trial described above (see Efficacy), the most common adverse reactions reported during combination therapy with lapatinib and capecitabine were diarrhea (60% vs. 39% with capecitabine monotherapy), hand-foot syndrome (49% for each group), nausea (44% vs. 42%), rash (27% vs. 15%), vomiting (26% vs. 24%), and fatigue (18% vs. 27%).9 Of note, the incidence of a ≥20% decrease in LVEF was the same (6%) in both treatment groups.7

Adverse events led to treatment discontinuation in similar proportions of patients in the combination and monotherapy groups (13% and 12%, respectively).9

The product monograph should be consulted for a more detailed discussion of warnings, precautions, and adverse effects associated with lapatinib.

DRUG INTERACTIONS

The manufacturer recommends avoiding (where practical) concomitant use of lapatinib with:

• inhibitors or inducers of CYP3A4 (due to risk of alterations in lapatinib exposure);

• substrates of CYP3A4 or CYP2C8 with narrow therapeutic windows (due to risk of increased substrate exposure); and

• other QT-prolonging drugs (due to risk of serious cardiac arrhythmias).7

Use of lapatinib is also discouraged with drugs that can disrupt electrolyte levels (e.g., loop, thiazide, and related diuretics; amphotericin B; high-dose corticosteroids),7 presumably because electrolyte disturbances are a risk factor for cardiac arrhythmias such as torsade de pointes.

Examples of many drugs that fall into the categories above, as well as further details regarding potential interactions with lapatinib, are provided in the product monograph.

DOSAGE, ADMINISTRATION & MONITORING

The recommended doses of lapatinib and capecitabine for use as combination therapy are as follows:7

• lapatinib: 1250 mg (five tablets) once daily every day (administered at least one hour before or after a low-fat meal);

• capecitabine: 2000 mg/m² (divided into two equal doses given q12h) on days 1 through 14 in a 21-day cycle (administered with food or within 30 minutes after food).

No dosage adjustment is recommended for patients with renal impairment (any degree); however, initial dosing modifications are suggested for those with severe hepatic impairment (Child-Pugh Class C) and those in whom concomitant use of a strong inhibitor or inducer of CYP3A4 is considered necessary. In addition, interruption (with or without subsequent dosage adjustment) or discontinuation of therapy is recommended for specified toxicities7 (see Product Monograph for details).

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No duration of treatment has been clearly defined, although it has been recommended that therapy continue until disease progression or intolerable adverse effects occur.8

Parameters that should be monitored with lapatinib therapy include LVEF (before starting treatment and periodically during treatment) and liver function (transaminases, bilirubin, and alkaline phosphatase; before starting treatment, every four to six weeks during treatment, and as clinically indicated). Consideration of obtaining baseline and on-treatment electrolyte levels and electrocardiograms with QT measurements is also suggested.7

AVAILABILITY AND COST

Tykerb is supplied as oral tablets that contain the equivalent of 250 mg lapatinib free base.7 The wholesale cost for a 30-day supply of drug at the recommended dosage is $3,718.88.11 The Tykerb Assistance Program (1-888-GSK-4-ALL) provides reimbursement coordination assistance for patients who have been prescribed lapatinib and capecitabine in combination (per the product monograph). Eligible patients experiencing financial hardship may apply through the program for assistance to cover the cost of lapatinib therapy.

DISCUSSION

The combination of lapatinib and capecitabine is associated with extended time to progression and progression-free survival (but not overall survival) in patients with HER2-positive metastatic breast cancer that has progressed despite treatment with trastuzumab-α, anthracycline-, and taxane-containing regimens. Nonetheless, the optimal strategy for treating such patients is unknown, and there are data to suggest that continuing trastuzumab with other chemotherapeutic agents (e.g., capecitabine) may also be a reasonable option.2,3 In fact, 2009 guidelines12 from the US National Comprehensive Cancer Network list both lapatinib and trastuzumab as options for patients with HER2-positive metastatic disease who have been previously treated with trastuzumab (see Box).

It is also uncertain as to the best management approach for patients whose disease progresses while on lapatinib and capecitabine. Some clinicians elect to continue lapatinib in combination with an alternative chemotherapy drug.4

Studies evaluating lapatinib in various breast cancer settings and in a variety of other malignancies that overexpress HER1 and/or HER2 are underway.5,6 Of particular interest is a large (estimated enrolment: 8,000) phase III study that is comparing trastuzumab, lapatinib, trastuzumab followed by lapatinib, and the combination of trastuzumab and lapatinib as adjuvant therapy in women with operable HER2-positive breast cancer.2,13 Hopefully, this study will provide the data necessary to help refine treatment for women with HER2-positive early-stage breast cancer.2

REFERENCES


7. GlaxoSmithKline Inc. Tykerb product monograph. Mississauga, ON; 2009 May 14 [date of revision].


Preferred agents for trastuzumab-exposed HER2-positive breast cancer12

- Lapatinib + capecitabine
- Trastuzumab + other first-line agents
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib
## NEW PRODUCTS/PRODUCT UPDATES

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<td>100 mg capsules; bottles of 120</td>
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